

10/069, 332

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : C12N 15/57, 15/63, 9/64, A61K 38/48, C07K 16/40, C12Q 1/37</p>	<p>A2</p>	<p>(11) International Publication Number: WO 00/53774</p> <p>(43) International Publication Date: 14 September 2000 (14.09.00)</p>																																																																																								
<p>(21) International Application Number: PCT/US00/06237</p> <p>(22) International Filing Date: 8 March 2000 (08.03.00)</p> <p>(30) Priority Data: 09/264,585 8 March 1999 (08.03.99) US</p> <p>(71) Applicant (for all designated States except US): NEUROCRINE BIOSCIENCES, INC. [US/US]; 10555 Science Center Drive, San Diego, CA 92121 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): KELNER, Gregory, S. [US/US]; 725 Muirlands Vista Way, La Jolla, CA 92037 (US). CLARK, Melody [US/US]; 7075 Charmant Drive #20, San Diego, CA 92122 (US). MAKI, Richard, A. [US/US]; 4175-174 Porte de Palmas, San Diego, CA 92122 (US).</p> <p>(74) Agents: CHRISTIANSEN, William, T. et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).</p>																																																																																										
<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published Without international search report and to be republished upon receipt of that report.</p>																																																																																										
<p>(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR</p> <div style="text-align: center; margin-top: 10px;"> <p>ADAM-TS Family</p> <table style="margin: auto; border-collapse: collapse;"> <thead> <tr> <th></th> <th style="text-align: center;">pro</th> <th style="text-align: center;">metallo</th> <th style="text-align: center;">dis</th> <th style="text-align: center;">TSP1</th> <th style="text-align: center;">spacer</th> <th style="text-align: center;">TSP</th> <th style="text-align: center;">subunits</th> </tr> </thead> <tbody> <tr> <td>ADAMTS 1/METH1</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 2/pNPI</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 3/KIAA0366</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 4/agg-1</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 5/agg-2</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 6</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 7</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 8/METH2</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>ADAMTS 9</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> <tr> <td>GN-1</td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 20px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> <td style="width: 40px; height: 10px; background-color: #cccccc;"></td> </tr> </tbody> </table> </div>				pro	metallo	dis	TSP1	spacer	TSP	subunits	ADAMTS 1/METH1								ADAMTS 2/pNPI								ADAMTS 3/KIAA0366								ADAMTS 4/agg-1								ADAMTS 5/agg-2								ADAMTS 6								ADAMTS 7								ADAMTS 8/METH2								ADAMTS 9								GN-1							
	pro	metallo	dis	TSP1	spacer	TSP	subunits																																																																																			
ADAMTS 1/METH1																																																																																										
ADAMTS 2/pNPI																																																																																										
ADAMTS 3/KIAA0366																																																																																										
ADAMTS 4/agg-1																																																																																										
ADAMTS 5/agg-2																																																																																										
ADAMTS 6																																																																																										
ADAMTS 7																																																																																										
ADAMTS 8/METH2																																																																																										
ADAMTS 9																																																																																										
GN-1																																																																																										
<p>(57) Abstract</p> <p>Novel members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.</p>																																																																																										

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

METALLOPROTEINASES AND METHODS OF USE THEREFOR

TECHNICAL FIELD

5 The present invention relates generally to compositions and methods for the treatment of conditions associated with undesirable levels of metalloproteinase activity. The invention is more particularly related to metalloproteinases and agents that modulate the activity of such metalloproteinases which may be used, for example, for the therapy of diseases characterized by neuroinflammation and/or
10 neurodegeneration, as well as autoimmune diseases, cancer and inflammation.

BACKGROUND OF THE INVENTION

 The ADAMs (A Disintegrin and Metalloproteinase Domain) are a family of proteins that have both a metalloproteinase domain and disintegrin domain. The
15 ADAMs are membrane anchored proteins that contain homology to snake venom metalloproteases (SVMPs) and disintegrins. This family of proteins now contains over 20 members that have a wide variety of important proteolytic and cell fusion functions. ADAM 17/TACE and ADAM 10/Kuz function as proteases that cleave membrane bound tumor necrosis factor (TNF) and the extracellular domain of Notch, respectively.
20 Other ADAM family members, such as ADAM 1/fertilin α , are proteolytically processed to remove the metalloprotease domain but retain the disintegrin domain. This protein has been shown to be essential for sperm-egg cell fusion.

 A closely related family called ADAMTS contains a thrombospondin domain in addition to the disintegrin and metalloproteinase domains. ADAMTS-1, for
25 example, is expressed in association with inflammatory processes and in a cachexigenic colon carcinoma cell line (see Kuno et al., *J. Biol. Chem.* 272:556-562, 1997; Kuno et al., *Genomics* 46:466-471, 1997). This protein appears to be secreted from the cell and subsequently associated with the extracellular matrix (ECM).

 While the function of ADAMTS-1 and many of the ADAM proteins is
30 not known, it has been shown that ADAM 17 (TACE) processes TNF from the surface of the cell (see Black et al., *Nature* 385:729-733, 1997). ADAM 10 (Kuzbanian) has

also been shown to cleave TNF from the cell surface (Rosendahl et al., *J. Biol. Chem.* 272:24588-24593, 1997). ADAM 10 may be involved in the cleavage of other cell surface proteins as well. In *Drosophila*, ADAM 10 has been reported to cleave the cell surface proteins Notch (Pan and Rubin, *Cell* 90:271-280, 1997) and Delta (Qi et al.,
5 *Science* 283:91-94, 1999). Based largely on these results it is thought that ADAMs proteases are involved in the cleavage of proteins, including growth factors, cytokines and proteoglycans, from the cell surface.

Metalloproteinase activity has been linked to cancer metastasis. The activity of metalloproteinases can contribute to the development of neurodegeneration
10 and inflammation as well. In order to develop agents capable of selectively modulating the activity of a metalloproteinase that contributes to a human disease, it is important to identify and characterize additional metalloproteinases, such as members of the ADAMTS family, and agents that modulate an activity of such metalloproteinases. The present invention fulfills this need and further provides other related advantages.

15

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides ADAMTS polypeptides, and methods employing such polypeptides. Within certain aspects, isolated polynucleotides that encode an ADAMTS polypeptide are provided. Certain ADAMTS
20 polynucleotides encode an ADAMTS polypeptide that comprises: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no
25 more than 10% of the consecutive residues of the ADAMTS protein. Such polynucleotides may, within certain embodiments, comprise a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.

Within related aspects, the present invention provides recombinant expression vectors comprising an ADAMTS polynucleotide, as well as host cells
30 transformed or transfected with such an expression vector.

The present invention further provides isolated antisense polynucleotides complementary to at least 20 consecutive nucleotides present within an ADAMTS polynucleotide.

Within further aspects, methods are provided for preparing an ADAMTS polypeptide, comprising the steps of: (a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and (b) recovering an ADAMTS polypeptide.

The present invention further provides isolated ADAMTS polypeptides comprising: (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein. Such an ADAMTS polypeptide may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. ADAMTS polypeptide may comprise an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are

present at no more than 10% of the consecutive residues of the ADAMTS protein; and
(b) a physiologically acceptable carrier.

Vaccines are also provided, comprising: (a) an ADAMTS polypeptide comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that
5 comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) a non-specific immune response enhancer.

10 Within further aspects, the present invention provides isolated antibodies, or antigen-binding fragments thereof, that specifically bind to an ADAMTS polypeptide comprising a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

The present invention further provides methods for screening for agents
15 that modulate ADAMTS protein expression or activity. Within certain such aspects, methods are provided for screening for an agent that modulates ADAMTS protein expression in a cell, comprising: (a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence
20 recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and (b) subsequently evaluating the effect of the candidate modulator on expression of an
25 ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell. Similar screens may be performed using a cell comprising an ADAMTS gene promoter operably linked to a reporter gene, and evaluating the effect of a candidate modulator on expression of the reporter gene.

Within further such aspects, methods are provided for screening for an
30 agent that modulates an ADAMTS protein activity, comprising: (a) contacting a

candidate modulator with an ADAMTS polypeptide, comprising: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein; and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and (b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

ADAMTS polynucleotides, polypeptides and modulating agents may be used for a variety of therapeutic applications. Within certain aspects, methods are provided herein for inhibiting neuroinflammation and/or neurodegeneration in a patient, comprising administering to a patient an agent that decreases an activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27. Certain such agents may inhibit expression of an endogenous ADAMTS gene or may bind to an ADAMTS protein.

Within related aspects, methods are provided for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration, comprising administering to a patient a pharmaceutical composition as described above, and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration. Such conditions include Alzheimer's disease, Parkinson's disease and stroke.

Methods are further provided for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis, comprising administering to a patient a pharmaceutical composition as described above and thereby alleviating one or more symptoms of a condition associated with neuroinflammation and/or neurodegeneration.

Within further aspects, methods are provided for treating a patient afflicted with an invasive tumor, a brain tumor or a brain injury, comprising administering to a patient an agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Methods are further provided for modulating ADAMTS expression and/or activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS activity, wherein the ADAMTS polypeptide comprises: (i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or (ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and thereby modulating ADAMTS expression and/or activity in the cell.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:1).

Figure 2 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-2 (SEQ ID NO:2).

Figures 3A-3B present a partial sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:3).

Figure 4 presents a partial predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-4 (SEQ ID NO:4).

Figures 5A and 5B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0605 (SEQ ID NO:5).

Figure 6 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0605 (SEQ ID NO:6).

5 Figures 7A and 7B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0366 (SEQ ID NO:7).

Figure 8 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0366 (SEQ ID NO:8).

10 Figures 9A and 9B present the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:9).

Figure 10 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-3 (SEQ ID NO:10).

Figures 11A and 11B present the sequence of a polynucleotide encoding the representative human metalloproteinase KIAA0688 (SEQ ID NO:11).

15 Figure 12 presents the predicted amino acid sequence of the representative human metalloproteinase KIAA0688 (SEQ ID NO:12).

Figure 13 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:13).

20 Figure 14 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-5 (SEQ ID NO:14).

Figure 15 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:15).

Figure 16 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-4 (SEQ ID NO:16).

25 Figures 17A-17G present a sequence alignment of human ADAMTS-1 (SEQ ID NO:28), ADAMTS-2 (SEQ ID NO:2), ADAMTS-3 (SEQ ID NO:10), ADAMTS-4 (SEQ ID NO:4), KIAA0688 (SEQ ID NO:12), KIAA0366 (SEQ ID NO:8) and KIAA0605 (SEQ ID NO:6).

30 Figure 18 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:17).

Figure 19 presents the predicted amino acid sequence of the representative bovine metalloproteinase ADAMTS-4 (SEQ ID NO:18).

Figure 20 presents the sequence of a polynucleotide encoding the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:19).

5 Figure 21 presents the predicted amino acid sequence of the representative bovine metalloproteinase KIAA0688 (SEQ ID NO:20).

Figure 22 presents the sequence of a polynucleotide encoding the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:21).

10 Figure 23 presents the predicted amino acid sequence of the representative human metalloproteinase ADAMTS-5 (SEQ ID NO:22).

Figure 24 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:23).

Figure 25 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-2 (SEQ ID NO:24).

15 Figure 26 presents the sequence of a polynucleotide encoding the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:25).

Figure 27 presents the predicted amino acid sequence of the representative rat metalloproteinase ADAMTS-3 (SEQ ID NO:26).

20 Figure 28 is a photograph depicting a coumassie blue-stained gel following electrophoresis of 500 micrograms brevican, previously incubated with and without ADAMTS-4 (TS-4) as indicated.

Figure 29 depicts the amino acid sequence of ADAMTS-9 (SEQ ID NO:27). The predicted signal sequence is underlined. The Zn binding, met turn, TSP 1 motif and TSP-1 like submotifs are shaded. Two potential furin cleavage sites are in parenthesis with the most likely cleavage site shaded. A potential "cysteine switch" amino acid is indicated with a star. The start of each domain is indicated with an arrow.

25 Figures 30A-30C illustrate the comparison of ADAMTS-9 to other ADAMTS family members. In Figure 30A, the domain structure of human ADAMTS 9 is compared to human ADAMTS 1-8, and also with the *C. elegans* GON-1 protein.
30 The pro-domain, metalloprotease domain, disintegrin-like domain, initial TSP type 1

repeat, spacer region, and TSP1 like submotifs are outlined. Figure 30B shows the consensus sequence for Zn binding in the metalloprotease domain (SEQ ID NO:30), along with the Zn binding site for various ADAM and ADAM-TS proteins (SEQ ID Nos: 42-48, 50) that have active metalloprotease domains for comparison to ADAMTS-9 (SEQ ID NO:49). Conserved residues are shaded. Figure 30C is a dendrogram showing the phylogenetic relationship between the protein sequence of the known ADAM-TS human family members and GON-1 from *C. elegans*.

Figure 31 is a photograph illustrating the tissue distribution pattern of ADAMTS-9 in human fetal and adult cDNA. PCR analysis of several human fetal and adult cDNAs was performed using specific primers to ADAMTS 9. Lanes 2 -16 are human adult tissue cDNAs and lanes 17 - 24 are human fetal cDNAs. Lane 25 is a no cDNA control. The expected product size for these ADAMTS 9 primers is 510 bp. The lower panel contains the same cDNA samples used as a template for PCR with G3PDH primers (expected product size is 1 kb).

Figures 32A and 32B illustrate the chromosomal localization of human ADAMTS-9 to 3p14.3-21.1. Figure 32A is a photograph showing the results of FISH analysis in which a genomic ADAMTS 9 probe hybridized to chromosome 3p. Figure 32B shows two ideograms illustrating the chromosomal position of ADAMTS-9 at 3p14.2-14.3. The International System for Human Cytogenetic Nomenclature 1995 was used.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to polypeptides comprising a member of the ADAMTS family of metalloproteinases, or a variant thereof. Such ADAMTS polypeptides are generally characterized by homology to a known ADAMTS protein, and by the presence of one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain, (c) an ECM domain and/or (d) a thrombospondin type I motif, which may be identified as described herein. The present invention further provides ADAMTS polynucleotides encoding such polypeptides and agents that modulate an activity of such polypeptides. ADAMTS

polypeptides, polynucleotides and/or modulating agents may generally be used for treating conditions associated with undesirable levels of metalloproteinase activity.

ADAMTS POLYNUCLEOTIDES

5 Any polynucleotide that encodes an ADAMTS polypeptide as described herein is encompassed by the present invention. Such polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a
10 polynucleotide may, but need not, be linked to other molecules and/or support materials.

 ADAMTS polynucleotides may comprise a native ADAMTS sequence (*i.e.*, an ADAMTS gene that can be found in an organism that is not genetically modified), or may comprise a variant of such a sequence. Native ADAMTS sequences
15 encompassed by the present invention include DNA and RNA molecules that comprise a sequence recited in any one of SEQ ID NOs:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 or 25 as well as homologues thereof from other species and other native ADAMTS sequences that may be identified based on homology to a sequence recited herein. Polynucleotide variants may contain one or more substitutions, additions, deletions
20 and/or insertions such that an ADAMTS activity of the encoded polypeptide is not diminished, relative to a native ADAMTS protein. The effect on an activity of the encoded polypeptide may generally be assessed as described herein. Preferred variants contain nucleotide substitutions, deletions, insertions and/or additions at no more than 30%, preferably at no more than 20% and more preferably at no more than 10%, of the
25 nucleotide positions. Certain variants are substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding an ADAMTS polypeptide (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5%
30 SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed

by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also within the scope of this invention.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention.

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense oligonucleotides may be synthesized directly, or cDNA constructs that can be transcribed into antisense RNA may be introduced into cells or tissues to facilitate the production of antisense RNA. Antisense oligonucleotides are preferably at least 20 nucleotides in length, preferably at least 30 nucleotides in length. A portion of a coding sequence or a complementary sequence may also be designed as a probe or primer to detect gene expression. Probes may be labeled by a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers are preferably 22-30 nucleotides in length.

ADAMTS polynucleotides may be prepared using any of a variety of techniques. For example, an ADAMTS polynucleotide may be amplified from cDNA prepared from cells that express an ADAMTS protein (*e.g.*, microglia, macrophages, myeloid cells, lymphocytes, astrocytes oligodendrocytes, glial cells, neurons, epithelial cells and/or endothelial cells). Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed

based on the sequences provided herein, and may be purchased or synthesized. An amplified portion may then be used to isolate a full length gene from a human genomic DNA library or from a suitable cDNA library, using well known techniques. Alternatively, a full length gene can be constructed from multiple PCR fragments.

5 ADAMTS polynucleotides may also be prepared by synthesizing oligonucleotide components (which may be derived from sequences provided herein), and ligating components together to generate the complete polynucleotide. One other approach is to screen a library with a synthesized oligonucleotide that hybridizes to an ADAMTS gene. Libraries may generally be prepared and screened using methods well known to

10 those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. It has been found, within the context of the present invention, that ADAMTS genes are expressed in glia. Accordingly, one suitable library is a microglia (e.g., rat) cDNA library. Other libraries that may be employed will be apparent to those

15 of ordinary skill in the art.

As noted above, polynucleotides comprising portions and other variants of native ADAMTS sequences are within the scope of the present invention. Such polynucleotides may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis.

20 Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding an ADAMTS polypeptide, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Variants may also be generated by mutagenesis or enzymatic digestion of native sequences. Certain polynucleotides may be used to prepare an encoded polypeptide, as

25 described herein. In addition, or alternatively, a polynucleotide may be administered to a patient such that the encoded polypeptide is generated *in vivo*.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather

30 than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional

bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.*, avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for polynucleotides for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

ADAMTS POLYPEPTIDES

As used herein, the term "ADAMTS polypeptide" encompasses amino acid chains of any length. For example, an ADAMTS polypeptide may comprise a full length endogenous (*i.e.*, native) ADAMTS protein. Such an ADAMTS polypeptide may consist entirely of a native ADAMTS sequence, or may contain additional heterologous sequences. Native ADAMTS proteins may generally be identified based on sequence homology to known ADAMTS protein sequences, such as the representative sequences provided herein, particularly within disintegrin, metalloproteinase and/or thrombospondin motifs. In general, a protein is considered to be an ADAMTS protein if at least 20 consecutive amino acid residues, preferably 40 consecutive amino acids, are identical to a known ADAMTS protein. Alternatively, or in addition, an ADAMTS protein may comprise at least 100 consecutive amino acids that are substantially similar to residues within a known ADAMTS metalloproteinase. "Substantial similarity," as used herein, refers to a sequence that is at least 50% identical, and preferably at least 80% identical.

An ADAMTS protein further comprises one or more of: (a) a disintegrin domain, (b) a zinc-dependent metalloproteinase domain and/or (c) a thrombospondin type I motif; and displays at least one, activity characteristic of such a domain or motif. In general a disintegrin domain serves as an integrin binding loop and has a sequence similar to AVN(E/D)CD (SEQ ID NO:29). Disintegrin domains can also contain the sequence RGD. The metalloproteinase domain is based on the presence of an extended catalytic site consensus sequence (HEXXHXXGXXHD; SEQ ID NO:30). It is thought that the three histidines bind the zinc, the glutamic acid is the catalytic base and the glycine allows an important structural turn (Stocker et al., *Protein Science* 4:823-840, 1995). The thrombospondin domain contains the sequence motif CSRTCG (SEQ ID NO:31).

Another domain that may be present within an ADAMTS protein is a domain that binds to the extracellular matrix. This has been referred to as the ECM domain and has the semiconserved sequence FREEQC (SEQ ID NO:32).

In certain embodiments, amino acid residues within a "substantially similar" region may contain primarily or entirely conservative substitutions. A conservative substitution is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry
5 would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity on polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine
10 and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys,
15 arg, his; and (5) phe, tyr, trp, his.

An ADAMTS polypeptide may comprise a portion of a native ADAMTS protein. Such a portion is preferably at least 20 consecutive amino acid residues in length, more preferably at least 50 consecutive amino acid residues in length. Within certain embodiments, the portion retains an ADAMTS activity that is not substantially
20 diminished relative to the full length ADAMTS protein. Certain ADAMTS polypeptides comprise a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

Alternatively, an ADAMTS polypeptide may comprise a variant of an ADAMTS protein or portion thereof. A "variant" is a polypeptide that differs in
25 sequence from a native ADAMTS protein only in substitutions, deletions, insertions and/or additions. Within certain embodiments, substitutions are made (if at all) at no more than 30%, preferably at no more than 20% and more preferably at no more than 10% of residues within a portion of a native ADAMTS protein, as described above. Substitutions are preferably conservative, as described above. Substitutions, deletions
30 and/or amino acid additions may be made at any location(s) in the polypeptide,

provided that the modification does not diminish at least one ADAMTS activity. Thus, a variant may comprise only a portion of a native ADAMTS sequence. In addition, or alternatively, variants may contain additional amino acid sequences (such as, for example, linkers, tags and/or ligands), preferably at the amino and/or carboxy termini.
5 Such sequences may be used, for example, to facilitate purification, detection or cellular uptake of the polypeptide.

Certain variants retain an activity of the native ADAMTS protein. In other words, the variant has a metalloproteinase activity; (2) functions as an integrin ligand (*i.e.*, binds to an integrin), as determined by any standard binding assay; and/or
10 (3) retains a functional thrombospondin motif. Such a variant may have an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein. In other words, the ADAMTS activity of the variant may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein.

Also encompassed by the present invention are splice variants of an ADAMTS protein. Such variants may have one or more of the domains described herein deleted, or one or more such domains may be replaced by a domain providing a different function. Such splice variants may be identified using amplification or hybridization techniques described herein.
15

Dominant negative forms of ADAMTS proteins are also provided. Such forms include fragments and variants of an ADAMTS protein that, when introduced to a cell expressing a native ADAMTS protein, inhibit an activity of the native protein. Inhibition of ADAMTS protein activity may be assessed as described herein.
20

In general, ADAMTS polypeptides may be prepared using any of a variety of techniques that are well known in the art. For example, polypeptides of the present invention may be prepared by expression of recombinant DNA encoding the polypeptide in cultured host cells. Preferably, the host cells are bacteria, yeast, insect or mammalian cells. The recombinant DNA may be cloned into any expression vector suitable for use within the host cell and transfected into the host cell using techniques well known to those of ordinary skill in the art. An expression vector generally contains
25
30

a promoter sequence that is active in the host cell. A tissue specific promoter may also be used, as long as it is activated in the target cell. Preferred promoters express the polypeptide at high levels.

Optionally, the construct may contain an enhancer, a transcription
5 terminator, a poly(A) signal sequence, a bacterial or mammalian origin of replication and/or a selectable marker, all of which are well known in the art. Enhancer sequences may be included as part of the promoter region used or separately. Transcription terminators are sequences that stop RNA polymerase-mediated transcription. The poly(A) signal may be contained within the termination sequence or incorporated
10 separately. A selectable marker includes any gene that confers a phenotype on the host cell that allows transformed cells to be identified. Such markers may confer a growth advantage under specified conditions. Suitable selectable markers for bacteria are well known and include resistance genes for ampicillin, kanamycin and tetracycline. Suitable selectable markers for mammalian cells include hygromycin, neomycin, genes
15 that complement a deficiency in the host (e.g. thymidine kinase and TK⁻ cells) and others well known in the art.

ADAMTS polypeptides may be expressed in transfected cells by culturing the cell under conditions promoting expression of the transfected polynucleotide. Appropriate conditions will depend on the specific host cell and
20 expression vector employed, and will be readily apparent to those of ordinary skill in the art. For commercially available expression vectors, the polypeptide may generally be expressed according to the manufacturer's instructions. Expressed polypeptides of this invention are generally isolated in substantially pure form. Preferably, the polypeptides are isolated to a purity of at least 80% by weight, more preferably to a
25 purity of at least 95% by weight, and most preferably to a purity of at least 99% by weight. In general, such purification may be achieved using, for example, the standard techniques of ammonium sulfate fractionation, SDS-PAGE electrophoresis, and/or affinity chromatography.

Such techniques may be used to prepare native polypeptides or variants
30 thereof. For example, variants of a native polypeptide may generally be prepared from

polynucleotide sequences modified via standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis, and sections of the DNA sequence may be removed to permit preparation of truncated polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptides and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

EVALUATION OF ADAMTS ACTIVITY

As noted above, native ADAMTS proteins and certain variants thereof possess ADAMTS activity. In other words, such polypeptides (1) possess metalloproteinase activity; (2) are capable of interacting with integrin and/or (3) retain a functional thrombospondin motif. Metalloproteinase activity may generally be evaluated by combining an ADAMTS polypeptide with a suitable substrate, and detecting proteinase activity using any standard technique (e.g., Western blot analysis). In general, a variant of an ADAMTS protein that contains a metalloproteinase domain is said to retain metalloproteinase activity if it displays metalloproteinase activity that is not substantially diminished relative to the metalloproteinase activity of the native

ADAMTS protein. In other words, such activity may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

The ability of an ADAMTS protein variant to interact with integrin may be assessed using standard binding assays to detect interaction with a purified recombinant integrin or a cell expressing one or more integrins, either naturally or as a result of transfection with genes encoding an integrin (*see Almeida et al., Cell 81:1095-1104, 1995; Chen et al., J. Cell Biol. 144:549-561, 1999*). Antibodies against various integrins can also be used to interfere with disintegrin-integrin binding and used to further demonstrate specificity of the interaction. In general, a variant of an ADAMTS protein is said to retain the ability to interact with an integrin if such interaction is not substantially diminished relative to the interaction between a native ADAMTS protein and the integrin. In other words, the level of such an interaction may be enhanced, unchanged or diminished by less than 10%, relative to the activity of the native ADAMTS protein.

Thrombospondins have been shown to function in cell adhesion, cell migration, cell proliferation and angiogenesis. A functional thrombospondin motif may be confirmed based on any assay designed to assess such a function. For examples, an ADAMTS protein may inhibit endothelial cell migration, or may inhibit angiogenesis (*e.g., in a rat cornea model; see Nishimori et al., Oncogene 15:2145-2150, 1997*). Alternatively, a functional thrombospondin motif may be detected using an assay to measure binding to CD36 (*see Dawson et al., J. Cell. Biol. 138:707-717, 1997*). Within any such assay, a variant of an ADAMTS protein is said to have a functional thrombospondin motif if the detected thrombospondin function is not substantially diminished relative to that of the native ADAMTS protein. In other words, the function may be enhanced, unchanged or diminished by less than 10%, relative to that of the native ADAMTS protein.

ADAMTS POLYPEPTIDE MODULATING AGENTS

The present invention further provides agents capable of modulating ADAMTS activity. Such agents may function by modulating ADAMTS transcription

or translation, by stabilizing or destabilizing an ADAMTS protein, or by directly inhibiting or enhancing an activity of an ADAMTS protein. Alternatively, an agent may interact with a substrate for the metalloproteinase or with an integrin involved in and interaction with the disintegrin domain of an ADAMTS protein. Preferably, a
5 modulating agent has a minimum of side effects and is non-toxic. For some applications, agents that can penetrate cells or that are targeted to interstitial spaces are preferred.

Modulating agents include substances that selectively bind to an ADAMTS protein. Such substances include antibodies and antigen-binding fragments
10 thereof (e.g., F(ab)₂, Fab, Fv, V_H or V_K fragments), as well as single chain antibodies, multimeric monospecific antibodies or fragments thereof and bi- or multi-specific antibodies and fragments thereof. Antibodies that bind to an ADAMTS protein may be polyclonal or monoclonal, and are specific for an ADAMTS polypeptide (i.e., bind to
15 such a peptide detectable within any appropriate binding assay, and do not bind to an unrelated protein in a similar assay under the same conditions). Preferred antibodies are those antibodies that function as modulating agents to inhibit or block an ADAMTS activity *in vivo*. Antibodies may also be employed within assays for detecting the level of ADAMTS protein within a sample.

Antibodies may be prepared by any of a variety of techniques known to
20 those of ordinary skill in the art (see, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988). In one such technique, an immunogen comprising the polypeptide is initially injected into a suitable animal (e.g., mice, rats, rabbits, sheep and goats), preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.
25 Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements
30 thereto. Briefly, these methods involve the preparation of immortal cell lines capable of

producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction.

Once a cell line, such as a hybridoma, expressing an antibody that specifically binds to an ADAMTS protein has been obtained, other chimeric antibodies and fragments thereof as described herein may be prepared. Using well known techniques, a cDNA molecule encoding the antibody may be identified.

Other modulating agents include peptides, and nonpeptide mimetics thereof, that specifically interact with one or more regions of an ADAMTS polypeptide. Such agents may generally be identified using any well known binding assay, such as a representative assay provided herein. For example, such modulating agents may be isolated using well known techniques to screen substances from a variety of sources, such as plants, fungi or libraries of chemicals, small molecules or random peptides.

Other modulating agents may function by inhibiting or enhancing transcription or translation of an ADAMTS gene. For example, modulating agents may include antisense polynucleotides (DNA or RNA), which inhibit the transcription of a native ADAMTS protein. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. Antisense technology can generally be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., *In Huber and Carr, Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes. Antisense polynucleotides are generally at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length.

Other agents may modulate transcription by interacting with an ADAMTS promoter. Such agents may be identified using standard assays, following isolation of an endogenous ADAMTS gene promoter region. One method for identifying a promoter region uses a PCR-based method to clone unknown genomic DNA sequences adjacent to a known cDNA sequence. This approach may generate a 5' flanking region, which may be subcloned and sequenced using standard methods. Primer extension and/or RNase protection analyses may be used to verify the transcriptional start site deduced from the cDNA.

To define the boundary of the promoter region, putative promoter inserts of varying sizes may be subcloned into a heterologous expression system containing a suitable reporter gene without a promoter or enhancer may be employed. Internal deletion constructs may be generated using unique internal restriction sites or by partial digestion of non-unique restriction sites. Constructs may then be transfected into cells that display high levels of ADAMTS protein expression. In general, the construct with

the minimum 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter.

To evaluate the effect of a candidate agent on ADAMTS gene transcription, a promoter or regulatory element thereof may be operatively linked to a reporter gene. Such a construct may be transfected into a suitable host cell, which may be used to screen, for example, a combinatorial small molecule library. Briefly, cells are incubated with the library (*e.g.*, overnight). Cells are then lysed and the supernatant is analyzed for reporter gene activity according to standard protocols. Compounds that result in a decrease in reporter gene activity are inhibitors of ADAMTS gene transcription.

For modulating agents that act directly on an ADAMTS protein, an initial screen to assess the ability of candidate agents to bind to such a protein may be employed, although such binding is not essential for a modulating agent. For identifying agents that bind to an ADAMTS polypeptide, any of a variety of binding assays may be employed, such as standard affinity techniques and yeast two-hybrid screens. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. An antibody or other modulating agent is said to "specifically bind" to an ADAMTS polypeptide if it reacts at a detectable level with such a polypeptide and does not react detectably with unrelated polypeptides. Such antibody binding properties may be assessed using, for example, an ELISA.

Screens for modulating agents that increase the rate of ADAMTS protein synthesis or stabilize ADAMTS protein may be readily performed using well known techniques that detect the level of ADAMTS protein or mRNA. Suitable assays include RNA protection assays, *in situ* hybridization, ELISAs, Northern blots and Western blots. Such assays may generally be performed using standard methods (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). For example, to detect mRNA encoding ADAMTS protein, a nucleic acid probe complementary to all or a portion of an ADAMTS gene sequence may be employed in a Northern blot analysis of mRNA prepared from suitable cells (*e.g.*, brain, lung, heart, spleen, spinal cord, testis, astrocytes or microglia).

To detect ADAMTS protein, a reagent that binds to the protein (typically an antibody) may be employed within an ELISA or Western assay. Following binding, a reporter group suitable for direct or indirect detection of the reagent is employed (*i.e.*, the reporter group may be covalently bound to the reagent or may be bound to a second molecule, such as Protein A, Protein G, immunoglobulin or lectin, which is itself capable of binding to the reagent). Suitable reporter groups include, but are not limited to, enzymes (*e.g.*, horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. Such reporter groups may be used to directly or indirectly detect binding of the reagent to a sample component using standard methods known to those of ordinary skill in the art.

To use such assays for identifying a modulating agent, the level of ADAMTS protein or mRNA is evaluated in cells (*e.g.*, astrocytes or microglia) treated with one or more candidate modulating agents. An increase or decrease in ADAMTS levels may be measured by evaluating ADAMTS mRNA and/or protein in the presence and absence of candidate modulating agent. In general, the amount of candidate modulator added in such screens ranges from about 1 pM to 1 μ M. A candidate that results in a statistically significant change in the level of ADAMTS mRNA and/or protein is a modulating agent.

Modulating agents that decrease ADAMTS levels generally inhibit ADAMTS activity. To further evaluate the effect on ADAMTS activity, an assay may be performed as described above in the presence and absence of modulating agent. Agents that bind to a substrate of an ADAMTS protein domain may also be identified using such assays. Modulating agents may generally be administered by addition to a cell culture or by the methods described below for *in vivo* administration.

25

ADAMTS POLYPEPTIDE AND MODULATING AGENT MODIFICATION AND FORMULATIONS

An ADAMTS polypeptide or modulating agent as described herein may, but need not, be linked to one or more additional molecules. In particular, as discussed below, it may be beneficial for certain applications to link multiple polypeptides and/or modulating agents (which may, but need not, be identical) to a support material, such as

30

a polymeric matrix or a bead or other particle, which may be prepared from a variety of materials including glass, plastic or ceramics. For certain applications, biodegradable support materials are preferred.

Suitable methods for linking an ADAMTS polypeptide or modulating agent to a support material will depend upon the composition of the support and the intended use, and will be readily apparent to those of ordinary skill in the art. Attachment may generally be achieved through noncovalent association, such as adsorption or affinity or, preferably, via covalent attachment (which may be a direct linkage or may be a linkage by way of a cross-linking agent).

It may be beneficial for certain applications to link an ADAMTS polypeptide or modulating agent to a targeting agent to facilitate targeting to one or more specific tissues. As used herein, a "targeting agent," may be any substance (such as a compound or cell) that, when linked to a polypeptide or modulating agent enhances the transport of the polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Targeting agents include antibodies or fragments thereof, receptors, ligands and other molecules that bind to cells of, or in the vicinity of, the target tissue. Known targeting agents include serum hormones, antibodies against cell surface antigens, lectins, adhesion molecules, tumor cell surface binding ligands, steroids, cholesterol, lymphokines, fibrinolytic enzymes and those drugs and proteins that bind to a desired target site. An antibody targeting agent may be an intact (whole) molecule, a fragment thereof, or a functional equivalent thereof. Linkage is generally covalent and may be achieved by, for example, direct condensation or other reactions, or by way of bi- or multi-functional linkers. Within other embodiments, it may also be possible to target a polynucleotide encoding a polypeptide or modulating agent to a target tissue, thereby increasing the local concentration. Such targeting may be achieved using well known techniques, including retroviral and adenoviral infection. To treat a patient afflicted with certain conditions (*e.g.*, neurodegenerative conditions), it may be beneficial to deliver an ADAMTS polypeptide, polynucleotide or modulating agent to the intracellular space. Such targeting may be achieved using well known

techniques, such as through the use of polyethylene glycol or liposomes, as described in Turrens, *Xenobiotica* 21:1033-1040, 1991.

For certain embodiments, it may be beneficial to also, or alternatively, link a drug to a polypeptide or modulating agent. As used herein, the term "drug" refers to any bioactive agent intended for administration to a mammal to prevent or treat a disease or other undesirable condition.

Within certain aspects of the present invention, one or more polypeptides, polynucleotides or modulating agents as described herein may be present within a pharmaceutical composition or vaccine. A pharmaceutical composition further comprises one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants and liposomes.

To prepare a pharmaceutical composition, an effective amount of one or more polypeptides, polynucleotides and/or modulating agents is mixed with a suitable pharmaceutical carrier. Solutions or suspensions used for parenteral, intradermal, subcutaneous or topical application can include, for example, a sterile diluent (such as water), saline solution, fixed oil, polyethylene glycol, glycerin, propylene glycol or other synthetic solvent; antimicrobial agents (such as benzyl alcohol and methyl parabens); antioxidants (such as ascorbic acid and sodium bisulfite) and chelating agents (such as ethylenediaminetetraacetic acid (EDTA)); buffers (such as acetates, citrates and phosphates). If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, polypropylene glycol and mixtures thereof. In addition, other pharmaceutically active ingredients and/or suitable excipients such as salts, buffers and stabilizers may, but need not, be present within the composition.

A pharmaceutical composition is generally formulated and administered to exert a therapeutically useful effect while minimizing undesirable side effects. The

number and degree of acceptable side effects depend upon the condition for which the composition is administered. For example, certain toxic and undesirable side effects that are tolerated when treating life-threatening illnesses, such as tumors, would not be tolerated when treating disorders of lesser consequence. The concentration of active
5 component in the composition will depend on absorption, inactivation and excretion rates thereof, the dosage schedule and the amount administered, as well as other factors that may be readily determined by those of skill in the art.

A polypeptide, polynucleotide or modulating agent may be prepared with carriers that protect it against rapid elimination from the body, such as time release
10 formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others known to those of ordinary skill in the art. Such formulations may generally be prepared using well known technology and
15 administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polynucleotide, polypeptide or modulating agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Preferably the formulation provides a relatively constant level of modulating agent release. The
20 amount of active component contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Pharmaceutical compositions of the present invention may be administered in a manner appropriate to the disease to be treated (or prevented).
25 Administration may be effected by incubation of cells *ex vivo* or *in vivo*, such as by topical treatment, delivery by specific carrier or by vascular supply. Appropriate dosages and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease and the method of administration. In general, an appropriate dosage and treatment
30 regimen provides the polypeptide, polynucleotide and/or modulating agent(s) in an

amount sufficient to provide therapeutic and/or prophylactic benefit (*i.e.*, an amount that ameliorates the symptoms or treats or delays or prevents progression of the condition). The precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by testing the compositions in model systems known in the art and extrapolating therefrom. Dosages may also vary with the severity of the condition to be alleviated. The composition may be administered one time, or may be divided into a number of smaller doses to be administered at intervals of time. In general, the use of the minimum dosage that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art, and for any particular subject, specific dosage regimens may be adjusted over time according to the individual need.

For pharmaceutical compositions comprising polynucleotides, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid, bacterial and viral expression systems, and colloidal dispersion systems such as liposomes. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal, as described above). The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993.

Various viral vectors that can be used to introduce a nucleic acid sequence into the targeted patient's cells include, but are not limited to, vaccinia or other pox virus, herpes virus, retrovirus, or adenovirus. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. Preferably, the retroviral vector is a derivative of a murine or avian retrovirus including, but not limited to, Moloney murine leukemia virus (MoMuLV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), and Rous Sarcoma Virus (RSV). A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a gene that

encodes the ligand for a receptor on a specific target cell (to render the vector target specific).

Viral vectors are typically non-pathogenic (defective), replication competent viruses, which require assistance in order to produce infectious vector particles. This assistance can be provided, for example, by using helper cell lines that contain plasmids that encode all of the structural genes of the retrovirus under the control of regulatory sequences within the LTR, but that are missing a nucleotide sequence which enables the packaging mechanism to recognize an RNA transcript for encapsulation. Such helper cell lines include (but are not limited to) Ψ2, PA317 and PA12. A retroviral vector introduced into such cells can be packaged and vector virion produced. The vector virions produced by this method can then be used to infect a tissue cell line, such as NIH 3T3 cells, to produce large quantities of chimeric retroviral virions.

Another targeted delivery system for polynucleotides is a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). RNA, DNA and intact virions can be encapsulated within the aqueous interior and delivered to cells in a biologically active form. The preparation and use of liposomes is well known to those of ordinary skill in the art.

THERAPEUTIC APPLICATIONS

As noted above, ADAMTS polynucleotides, polypeptides and modulating agents may generally be used for the therapy of diseases characterized by neuroinflammation or neurodegeneration. In general, ADAMTS metalloproteinases are believed to function in cleaving proteins from cell surfaces (which may be surfaces of cells that synthesize the metalloproteinase or other cells). Pharmaceutical compositions as provided herein may be administered to a patient, alone or in combination with other therapies, to treat or prevent neurodegenerative diseases such as Alzheimer's disease,

Parkinson's disease or stroke. Pharmaceutical compositions provided herein may also be beneficial for therapy of conditions related to cell proliferation, cell migration, inflammation or angiogenesis. Such conditions include cancer, arthritis and autoimmune diseases.

5 Modulation of an ADAMTS function, either *in vitro* or *in vivo*, may generally be achieved by administering a modulating agent that inhibits ADAMTS transcription, translation or activity. In some instances, however, the ADAMTS activity may be lower than is desired. In such cases, polynucleotides, polypeptides and/or modulating agents that enhance ADAMTS activity may be administered. The activity
10 of an endogenous ADAMTS protein within a cell may be increased by, for example, inducing expression of the ADAMTS gene and/or administering a modulating agent that enhances ADAMTS activity. Each of these methods may be performed using mammalian cells in culture or within a mammal, such as a human.

 Certain ADAMTS polypeptides may be used to cleave the proteoglycan
15 brevican. Brevican is a brain specific proteoglycan. The secreted form of brevican is upregulated in response to CNS injury and has been implicated in reactive gliosis, and a cleaved form may be important for tumor invasion (*see* Zhang et al., *J. Neuroscience* 18:2370-76, 1998). Thus, brevican cleavage appears to be important in brain injury and gliomas. Modulating agents that inhibit the ability of such ADAMTS polypeptides to
20 cleave brevican may be used to treat brain injuries, brain tumors and other invasive tumors.

 Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by
25 injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. A suitable dose is an amount of a compound that, when administered as described above, is capable of causing modulation of an ADAMTS activity that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared
30 to non-vaccinated patients. In general, an appropriate dosage and treatment regimen

provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. In general, 5 suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

DIAGNOSTIC APPLICATIONS

In a related aspect of the present invention, kits for detecting ADAMTS 10 proteins are provided. Such kits may be designed for detecting the level of ADAMTS protein or nucleic acid encoding an ADAMTS protein within a sample. In general, the kits of the present invention comprise one or more containers enclosing elements, such as reagents or buffers, to be used in the assay. A kit for detecting the level of ADAMTS protein or nucleic acid typically contains a reagent that binds to the ADAMTS protein, 15 DNA or RNA. To detect nucleic acid, the reagent may be a nucleic acid probe or a PCR primer. To detect protein, the reagent is typically an antibody. A kit may also contain a reporter group suitable for direct or indirect detection of the reagent as described above.

The following Examples are offered by way of illustration and not by 20 way of limitation.

EXAMPLES

Example 15 Preparation of Novel ADAMTS Family Members

This Example illustrates the cloning of cDNA molecules encoding members of the ADAMTS family of metalloproteinases based on induction of expression in rat glial cells by aggregated beta amyloid.

Subtractive hybridization was performed as described (Kelner and Maki.
10 *Methods in Molecular Medicine, vol 22: Neurodegeneration Methods and Protocols*,
Eds J. Harry and H.A. Tilson, Human Press Inc., Totowa, NJ). Briefly, rat glial cells
were cultured and treated with aggregated beta amyloid. After 24 hours, RNA was
prepared from these cells and from control cells that were not treated with beta amyloid.
Genes expressed in the activated cells but not the control cells were sequenced. This
15 screen identified rat ADAMTS-3 (cDNA and encoded protein sequences shown in
Figure 26 (SEQ ID NO:25) and Figure 27 (SEQ ID NO:26), respectively). The rat
cDNA was used to screen a human cDNA library and resulted in the isolation of human
ADAMTS-3. ADAMTS-3 is 2,866 nucleotides in length (Figures 9A and 9B; SEQ ID
NO:9) and codes for a putative protein that is 955 amino acids in length (Figure 10;
20 SEQ ID NO:10). ADAMTS-3 contains a metalloproteinase domain, a disintegrin
domain, thrombospondin motifs and an ECM domain.

Example 225 Preparation of Novel ADAMTS Family Members using Degenerate PCR

This Example illustrates the use of degenerate PCR to clone partial cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

PCR was performed using rat microglia cDNA and degenerate oligonucleotides derived from an analysis of the sequence from ADAMTS-1 and
30 ADAMTS-3. Degenerate primers were designed based on common sequences between

these two genes. The original degenerate primers were designed based on a small region of these two genes that was cloned. One primer had the sequence 5'-TTYMGNGARGARCARTGY-3' (SEQ ID NO:33), while the other primer had the sequence 5'-RCANAYNCCRCAYTTTRTC-3' (SEQ ID NO:34). The PCR conditions
5 were annealing at 47°C for 1 minute, 72°C extension for 2 minutes and 94°C denaturation for 30 seconds.

Following PCR samples were fractionated by gel electrophoresis and fragments of the expected size were cloned into the vector pCRScript and sequenced. One amplified cDNA molecule was designated rat ADAMTS-2 (Figure 24; SEQ ID
10 NO:23), and the encoded protein has the predicted sequence shown in Figure 25 (SEQ ID NO:24). This cDNA was used to screen a human cDNA library, from which human ADAMTS-2 was identified. Human ADAMTS-2 has the sequence shown in Figure 1 (SEQ ID NO:1), and appears to encode the protein recited in Figure 2 (SEQ ID NO:2).

Rat ADAMTS-4 was isolated using the PCR approach and is a
15 polynucleotide having the sequence shown in Figures 3A and 3B (SEQ ID NO:3), which appears to encode the protein recited in Figure 4 (SEQ ID NO:4). For rat ADAMTS-4 the metalloproteinase domain begins at amino acid 260(R), the disintegrin domain begins at residue 487(Q), a thrombospondin motif begins at residue 570(W) and an ECM domain begins at residue 621(C). The rat ADAMTS-4 sequence was used to
20 screen a human cDNA library and human ADAMTS-4 was isolated. Human ADAMTS-4 is 1455 nucleotides in length (Figure 15; SEQ ID NO:15) and codes for a putative protein that is 485 amino acids in length (Figure 16; SEQ ID NO:16). The disintegrin domain in human ADAMTS-4 begins at amino acid 39(E), the start of the first thrombospondin repeat is at amino acid 124(W) and the start of another
25 thrombospondin repeat is at amino acid 479(C). Bovine ADAMTS-4 cDNA has the sequence shown in Figure 18 (SEQ ID NO:17), encoding the predicted amino acid sequence shown in Figure 19 (SEQ ID NO:18).

Rat ADAMTS-5 is a cDNA molecule with the sequence shown in Figure 13 (SEQ ID NO:13), encoding the amino acid sequence shown in Figure 14 (SEQ ID

NO:14). The human ADAMTS cDNA and protein sequences are shown in Figure 22 (SEQ ID NO:21) and Figure 23 (SEQ ID NO:22), respectively.

ADAMTS-4 was further shown to cleave the brain-specific proteoglycan brevican. Five hundred micrograms of purified brevican was cleaved with 500
5 micrograms of human ADAMTS-4 and incubated overnight at 37°C. The cleavage reaction was vacuum dried and resuspended in SDS sample loading dye for running on a 4-20% SDS polyacrylamide gel. Equal amounts of cleaved and uncleaved brevican were added to the gel. After electrophoresis the gel was stained with Coumassie Blue to visualize the protein bands. The results, presented in Figure 30, show that brevican is
10 cleaved upon incubation with ADAMTS-4.

Example 3

Identification of ADAMTS Family Members using Database Searches

15 This Example illustrates the use of database searches to identify cDNA molecules encoding members of the ADAMTS family of metalloproteinases.

To identify additional members of the ADAMTS family, the GenBank database was searched for sequences similar to ADAMTS-1 and ADAMTS-3. This search retrieved KIAA0605 (Figures 5A and 5B; SEQ ID NO:5), which appears to
20 encode a protein of 951 amino acids (Figure 6; SEQ ID NO:6). The coding sequence contains thrombospondin motifs, but no metalloproteinase or disintegrin domains have been identified. A thrombospondin motif begins with amino acid 50(W). Six additional thrombospondin motifs were found beginning with amino acid 568(K). The domain that binds to the extracellular matrix begins with amino acid 105(C).

25 Also retrieved was KIAA0366 (Figures 7A and 7B; SEQ ID NO:7), which appears to encode a protein of 951 amino acids (Figure 8; SEQ ID NO:8), including metalloproteinase and disintegrin domains, as well as thrombospondin motifs. For KIAA0366, the metalloproteinase domain begins with amino acid 241(T), the disintegrin domain begins with amino acid 460(D), a thrombospondin domain is present
30 beginning at position 544(W) and another thrombospondin repeat occurs at position

842(W). The ECM domain begins at amino acid 597(C) and contains the semiconserved sequence FREEQC (SEQ ID NO:32). KIAA0366 does not appear to have a transmembrane domain, and therefore is likely to encode a secreted protein.

An additional sequence identified in this search was KIAA0688 (Figures 11A and 11B; SEQ ID NO:11), which appears to encode the protein shown in Figure 12 and SEQ ID NO:12. This gene codes for a protein with a metalloproteinase domain beginning at amino acid 245(R), a disintegrin domain beginning at amino acid 465(E), a thrombospondin motif at position 550(W), an ECM domain at position 601(C) and two additional thrombospondin motifs at position 905(W). A bovine KIAA0688 cDNA sequence is shown in Figure 20 (SEQ ID NO:19), and the predicted amino acid sequence of the encoded protein is shown in Figure 21 (SEQ ID NO:20).

Figures 17A-17G present an alignment of the ADAMTS protein sequences described herein, along with ADAMTS-1.

Example 4

Identification and Characterization of ADAMTS-9

This Example illustrates the cloning and characterization of the ADAMTS/metalloproteinase family member designated herein as ADAMTS-9.

A small fragment of the rat ADAMTS-9 gene was initially cloned from a beta amyloid-treated (35 µg/ml aggregated Aβ 1-42) rat astrocyte cDNA library. DNA sequence analysis was performed using a PCR procedure employing fluorescent dideoxynucleotides and a model ABI-377 automated sequencer (PE Biosystem). BLAST sequence analysis revealed low homology at the protein level to the spacer region of the murine ADAMTS-1 gene.

This clone was labeled with [α -³²P]dCTP using the Prime It II kit (Stratagene) and used to screen a human spinal cord phage library (Clontech) according to the manufacturer's instructions. Positive plaques were purified and lambda DNA prepared (Qiagen). Several overlapping clones were sequenced that had homology to the original rat clone. In order to determine the 5' and 3' ends of the gene RACE (rapid

amplification of cDNA ends) analysis was performed using Marathon Ready placenta and fetal cDNA libraries (Clontech) with SMART primers (Clontech). Overlapping sequence was used to confirm the full length clone. The full length protein sequence of human ADAMTS-9 is shown in Figure 29. The 5' end of the clone contains a
5 methionine codon within a good Kozak consensus for translation initiation. A signal peptide sequence is located just downstream of this methionine in the translated ORF, and the size of the pro-domain is similar to that of other ADAM-TS family members. Therefore, this appears to be the starting methionine of ADAMTS-9.

The overall protein sequence of ADAMTS-9 is similar to that of the
10 other ADAM-TS proteins. All of these family members have a pro-domain, metalloprotease domain, disintegrin-like domain, thrombospondin domain, spacer region, and a variable number of a thrombospondin-like submotifs at the carboxyl-terminal end of the protein (Figure 32A). Like other ADAM-TS family members, ADAMTS 9 contains an amino-terminal signal peptide sequence and lacks a
15 transmembrane domain.

Among the 23 ADAM family members, 10 are predicted to be active proteases based on the sequence of their Zn binding catalytic sites (Black and White, *Curr. Opin. Cell. Biol* 10:654-659, 1998). The consensus catalytic sequence site based on ADAM and snake venom metalloproteases is HEXGHXXGXXHD (SEQ ID NO:51).
20 The ADAM-TS family of proteins has homology to this consensus sequence except at the second conserved glycine. ADAMTS 9 has an asparagine at this conserved glycine site in the helix. Two other ADAM-TS proteins, ADAMTS-1 and ADAMTS-4, also have an asparagine in this position instead of glycine (Figure 32B). This suggests that ADAMTS-9, line ADAMTS-1 and ADAMTS-4, may have an active metalloprotease
25 domain.

It has been proposed that an invariant cysteine residue in the pro-domain of MMP and ADAM proteins coordinates the catalytic Zn ion in the metalloprotease domain, thus maintaining the protease in an inactive state (Loechel et al., *J. Biol Chem.* 274:13427-33, 1999). Once the pro-domain is cleaved this interaction is interrupted and
30 the protease is activated by a "cysteine switch" mechanism. A proposed cysteine switch

residue in ADAMTS-9 is marked in Figure 29 by a star. Proteolytic processing of the pro-domain of ADAM and ADAM-TS proteins is believed to occur by furin endopeptidases in the Golgi. ADAMTS-9 contains two potential furin cleavage sites (consensus RX(K/R)R; SEQ ID NO:35) at the end of the pro-domain (see Figure 29).

- 5 Based on the sequence of mature murine *ADAMTS-1*, the second furin cleavage site is most likely used in ADAMTS-9 (resulting amino-terminus FLSYPR).

Following the metalloprotease domain, ADAMTS-9 contains a cysteine-rich region that has homology to the disintegrin domain in snake venom metalloprotease and ADAMs. Next, all of the ADAM-TS family members contain an
10 internal TSP1 motif that has the two conserved heparin binding segments: W(S/G)XWSXW (SEQ ID NO:36) and CSVTCG (SEQ ID NO:37). Separating the internal TSP1 motif and the carboxy terminal TSP1-like submotifs is a variable length spacer region. As seen in Figure 32A, most ADAM-TS family members have between one and three TSP1-like submotifs at the end of the protein. However at the extremes
15 are ADAMTS 3 which has no TSP1-like motifs and *C. elegans* GON-1 which has 17 of these motifs. ADAMTS-9 contains one internal TSP1 motif and three TSP-1 like submotifs at the carboxyl end (Figure 30A). A possible role for ADAMTS 9 in the adult is suppression of angiogenesis through the carboxy-terminal TSP1 motifs.

Overall, the predicted mature forms of the ADAM-TS proteins show 20-
20 40% similarity to each other. Interestingly, by BLAST analysis ADAMTS-9 shows as much homology to *C. elegans* GON-1 as to other human ADAM-TS, suggesting that ADAMTS 9 may be the human homologue of GON-1. The dendrogram in Figure 30C (prepared with the MegAlign program (DNASTar)) shows the relationship between the known human ADAM-TS members, ADAMTS 9, and GON-1.

25 The expression pattern of ADAMTS 9 was examined in a variety of human adult and fetal tissues using RT-PCR. For tissue distribution analysis, human multiple tissue cDNA panels I and II were purchased from Clontech. RT-PCR was performed using a touchdown procedure where the annealing temperature was dropped from 63°C to 57°C over 10 cycles then kept at 57°C for 20 cycles. The sense primer
30 was CAGGGGAAACAGACGATGACAACT (SEQ ID NO:38) and the antisense

primer was TGCGGTAACCCAAGCCACACT (SEQ ID NO:39). Expected product size was 510 bp. Control primers to glyceraldehyde-3-phosphate dehydrogenase (G3PDH) were supplied by Clontech--expected size is about 1 kb.

As seen with other ADAM-TS genes, Northern blot analysis showed
5 very low levels of expression. Therefore a more sensitive RT-PCR procedure was used. The cDNA panels used were normalized to the mRNA expression levels of several different housekeeping genes to ensure accurate assessment of tissue specificity. ADAMTS-9 was found in ovary, pancreas, heart, kidney, lung, placenta, and strikingly in all fetal tissues examined (Figure 31), suggesting a possible role in development. In
10 addition, using hybridization to cDNA libraries we have identified ADAMTS-9 in adult spinal cord and brain. However, ADAMTS-9 was not detected in colon, leukocyte, prostate, small intestine, testis, liver, skeletal muscle, spleen or thymus (Figure 31). Expression of the G3PDH housekeeping gene in all cDNAs tested is shown as a control for template integrity and the RT-PCR procedure. One notable difference in the
15 expression pattern of ADAMTS-9 compared to other ADAMTS genes is the presence of ADAMTS-9 in the adult kidney. This is of interest since the chromosomal locus containing ADAMTS-9 is often deleted in renal tumors.

A genomic clone of ADAMTS 9 was obtained by screening a human P1 library and used for FISH analysis (Genome Systems). Briefly, the human ADAMTS-9
20 genomic clone was labeled with digoxigenin dUTP by nick translation. Labeled probe was combined with sheared human DNA and hybridized to normal metaphase chromosomes derived from PHA stimulated peripheral blood lymphocytes in a solution containing 50% formamide, 10% dextran sulfate and 2X SSC. Specific hybridization signals were detected by incubating the hybridized slides in fluoresceinated
25 antidigoxigenin antibodies followed by counterstaining with DAPI for one-color experiments. Probe detection for two-color experiments was accomplished by incubating the slides in fluoresceinated antidigoxigenin antibodies and Texas red avidin followed by counterstaining with DAPI. A total of 80 metaphase cells were analyzed with 70 exhibiting specific labeling. Initial FISH experiments resulted in specific
30 labeling of the short arm of chromosome 3. Measurement of 10 specifically labeled

chromosome 3's demonstrated that ADAMTS-9 is located at a position which is 30% the distance from the centromere to the telomere of chromosome arm 3p, an area which corresponds to 3p14.3-21.1 (Figures 32A and 32B). Since deletions and other rearrangements of this locus are frequent and early events in the pathogenesis of a number of human cancers (including renal cell carcinoma, breast cancers, uterine cervical carcinoma and vulvar carcinomas, this region may contain one or more tumor suppressor genes.

The chromosomal localization of the human ADAMTS 9 locus was independently confirmed by PCR analysis of the Stanford G3 radiation hybrid mapping panel. The G3 hybrid mapping panel (Stewart et al., *Genomic Res.* 7:422-433, 1997) containing 83 radiation hybrid DNA, as well as human and hamster control DNAs was obtained from Research genetics Inc. (Huntsville, Alabama). The human chromosome content of each somatic cell hybrid was established by the Stanford Human Genome Center using more than 10,000 STSs derived from random genetic markers and expressed tagged sequences (<http://www-shgc.stanford.edu/Mapping/rh/>). PCR reactions were carried out in a 10 µl reaction volume containing 25 ng DNA template, 25 µm deoxynucleotide triphosphates, 20 pmol of each oligonucleotide primer, 0.5 U of Taq polymerase (Boehringer Mannheim), 2.5 mM MgCl₂, 50 mM KCl and 10 mM Tris-HCl (pH 8.3). The sense primer is GTGCGCTGGGTCCCTAAATAC (SEQ ID NO:40) which is in the coding sequence and the antisense primer is AAAATCACAGGTTGGCAGCGG (SEQ ID NO:41) which is in an intronic sequence. Thirty cycles of PCR were performed. Ten cycles consisted of denaturing at 94°C for 15 seconds, annealing at 62°C for 30 seconds, going down 0.5°C each cycle and extension at 72°C for 30 seconds. Twenty more cycles were performed using the same denaturing and extension conditions and keeping the annealing at 57°C for 30 seconds. PCR was proceeded by a 2 min incubation at 94°C and followed by a 72°C final soak for 10 minutes. Amplified products were electrophoresed through a 2% agarose gel and visualized by ethidium bromide staining. The resulting PCR product was a 302 bp human specific fragment. The presence or absence of the ADAMTS 9 product was scored for each of the somatic cell hybrids. The results were submitted to the Stanford

Radiation Hybrid Server via the internet (<http://www-shgc.stanford.edu>) and the completed data were returned to us. ADAMTS 9 was linked to the ordered markers SHGC-33668 with a LOD score of 11.47 and SHGC-20118 (D3S3571) with a LOD score of 11.06. The results confirm localization of ADAMTS 9 to the short arm of chromosome 3 and place ADAMTS-9 within the context of established maps. Furthermore SHGC-20118 (D3S3571) has been mapped to 3p14.2, placing ADAMTS-9 closer to the 14.2-14.3 region of chromosome 3. This location is interesting in that it contains a well characterized breakpoint for translocations common in hereditary renal cell carcinomas.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

CLAIMS

1. An isolated polynucleotide that encodes an ADAMTS polypeptide, wherein the polypeptide comprises:
 - (a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or
 - (b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.
2. A polynucleotide according to claim 1, wherein the polynucleotide comprises a sequence recited in any one of SEQ ID NOs:1, 3, 9, 13, 15, 17, 21, 23 or 25.
3. A polynucleotide according to claim 1, wherein substitutions, if any, are present at no more than 5% of the consecutive residues of the ADAMTS protein.
4. A polynucleotide according to claim 1, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.
5. A recombinant expression vector comprising a polynucleotide according to claim 1.
6. A host cell transformed or transfected with an expression vector according to claim 5.
7. An isolated antisense polynucleotide complementary to at least 20 consecutive nucleotides present within a polynucleotide according to claim 1.

8. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell transformed or transfected with an expression vector comprising a polynucleotide that encodes an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the step of culturing is performed under conditions promoting expression of the polynucleotide sequence; and

(b) recovering an ADAMTS polypeptide.

9. A method for preparing an ADAMTS polypeptide, the method comprising:

(a) culturing a host cell according to claim 6 under conditions promoting expression of the polynucleotide; and

(b) recovering an ADAMTS polypeptide.

10. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27; or

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

11. An ADAMTS polypeptide according to claim 10, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

12. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:2, 4, 10, 14, 16, 18, 22, 24, 26 or 27.

13. An isolated ADAMTS polypeptide comprising:

(a) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20

(b) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein.

14. An ADAMTS polypeptide according to claim 13, wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein.

15. An ADAMTS polypeptide according to claim 13, wherein the polypeptide comprises at least 40 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

16. A polypeptide comprising an amino acid sequence recited in any one of SEQ ID NOs:6, 8, 12, or 20.

17. A pharmaceutical composition comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a physiologically acceptable carrier.

18. A vaccine comprising:

(a) an ADAMTS polypeptide comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) a non-specific immune response enhancer.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an ADAMTS polypeptide that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27.

20. A method for screening for an agent that modulates ADAMTS protein expression in a cell, comprising:

(a) contacting a candidate modulator with a cell expressing an ADAMTS polypeptide, wherein the polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein

substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein; and

(b) subsequently evaluating the effect of the candidate modulator on expression of an ADAMTS mRNA or polypeptide, and therefrom identifying an agent that modulates ADAMTS protein expression in the cell.

21. A method for screening for an agent that modulates an ADAMTS protein activity, comprising:

(a) contacting a candidate modulator with an ADAMTS polypeptide, comprising:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and wherein the step of contacting is carried out under conditions and for a time sufficient to allow the candidate modulator to interact with the polypeptide; and

(b) subsequently evaluating the effect of the candidate modulator on an ADAMTS activity of the polypeptide, and therefrom identifying an agent that modulates an activity of an ADAMTS protein.

22. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neuroinflammation in a patient.

23. An agent according to claim 22, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

24. An agent according to claim 22, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

25. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for inhibiting neurodegeneration in a patient.

26. An agent according to claim 25, wherein ADAMTS activity is decreased by inhibiting expression of an endogenous ADAMTS gene.

27. An agent according to claim 25, wherein ADAMTS activity is decreased by administering a modulating agent that binds to an ADAMTS protein.

28. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for method for treating a patient afflicted with a condition associated with neuroinflammation and/or neurodegeneration.

29. A composition according to claim 28, wherein the condition is selected from the group consisting of Alzheimer's disease, Parkinson's disease and stroke.

30. A method for modulating ADAMTS activity in a cell, comprising contacting a cell expressing an ADAMTS polypeptide with an effective amount of an agent that modulates ADAMTS protein activity or expression, wherein the ADAMTS polypeptide comprises:

(i) at least 50 consecutive amino acid residues of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27; or

(ii) a variant of any of the foregoing amino acid sequences that differs in one or more substitutions, deletions, additions and/or insertions, wherein substitutions, if any, are present at no more than 10% of the consecutive residues of the ADAMTS protein;

wherein the polypeptide has an ADAMTS activity that is not substantially diminished relative to the ADAMTS protein;

and thereby modulating ADAMTS activity in the cell.

31. A pharmaceutical composition according to claim 17, for use in the manufacture of a medicament for treating a patient afflicted with a condition associated with cell proliferation, cell migration, inflammation and/or angiogenesis.

32. A composition according to claim 31, wherein the condition is selected from the group consisting of cancer, arthritis and autoimmune diseases.

33. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with an invasive tumor.

34. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain tumor.

35. An agent that decreases expression or activity of an ADAMTS protein that comprises a sequence recited in any one of SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20,

22, 24, 26 or 27, for use in the manufacture of a medicament for treating a patient afflicted with a brain injury.

36. An agent according to any one of claims 33-35, wherein the ADAMTS protein comprises a sequence recited in SEQ ID NO:16.

1/39

AGGACCAAGCGTTTGTGTCTGAGGCGCGCTTCGTGGAGACGCTGCTGGTGGCCGATGCGTCCATGGCTGCCTTCTACGG
GGCCGACCTGCAGAACCACATCCTGACGTTAATGTCTGTGGCAGCCCGAATCTACAAGCAGCCAGCATCAAGAATTCCA
TCAACCTGATGGTGGTAAAAGTGCTGATCGTAGAAGATGAAAAATGGGGCCAGAGGTGTCCGACAATGGGGGGCTTACA
CTGCGTAACCTTCTGCAACTGGCAGCGGCGTTTCAACCAGCCAGCGACCGGCACCCAGAGCACTACGACACGGCCATCCT
GCTCACCAGACAGAACTTCTGTGGGCAGGAGGGGCTGTGTGACACCTGGGTGTGGCAGACATCGGGACCATTTGTGACC
CCAACAAAAGCTGCTCCGTGATCGAGGATGAGGGGCTCCAGGCGGCCACACCTGGCCCATGAACTAGGGCACGTCTC
AGCATGCCCCACGACGACTCCAAGCCCTGCACACGGCTCTTCGGGCCATGGGCAAGCACCAGTGATGGCACCCTGTT
CGTCCACCTGAACCAGACGCTGCCCTGGTCCCCCTGCAGCGCCATGTATCTCACAGAGCTTCTGGACGGCGGGCACGGAG
ACTGTCTCCTGGATGCCCCCTGTGCGGCCCTGCCCTCCCCACAGGCTCCCGGGCCGATGGCCCTGTACCAGCTGGAC
CAGCAGTGCAGGCAGATCTTGGGCCGATTTCGCCACTGCCCCAACACCTCTGCTCAGGACGTCTGCGCCAGCTTTG
GTGCCACACTGATGGGGTGAGCCCTGTGCCACAGAAATGGCAGCCTGCCCTGGGTGACGGCACGCCGTGCGGGC
CTGGGCACCTCTGCTCAGAAGGCAGCTGTCTACCTGAGGAGGAAGTGAGAGGCCCAAGCCGTGGTAGATGGAGGCTGG
GCACCGTGGGGACCTGGGGAGAATGTTCTCGGACCTGTGGAGGAGGAGTACAGTTTTACACCGTGAGTGCAAGGACCC
CGAGCCTCAGAATGGAGGAAGATACTGCCTGGGTGCGAGAGCCAAGTACCAGTCATGCCACAGGAGGAATGCCCCCTG
ACGGGAAAAGCTTCAGGGAGCAGCAGTGTGAGAAGTATAATGCCTACAATTACACTGACATGGACGGGAATCTCCTGCAG
TGGGTCCCCAAGTATGCTGGGGTGTCCCCCGGGACCGCTGCAAGTTGTTCTGCCGAGCCCGGGGAGGAGCGAGTTCAA
AGTGTTCGAGGCCAAGGTGATTGATGGCACCTGTGTGGGCCAGAAACACTGGCCATCTGTGTCCGTGGCCAGTGTGTCA
AGGCCGGCTGTGACCATGTGGTGGACTCGTTTTGGAAGCTGGACAAATGCGGGGTGTGTGGGGGAAAGGCAACTCCTGC
AGGAAGGGCTCGGGTCCCTCACCCCCACCAATTATGGCTACAATGACATTGTACCATCCCAGCTGGTGCCACTAATAT
TGACGTGAAGCAGCGGAGCCACCCGGGTGTGCAGAACGATGGGAACCTACCTGGCGCTGAAGACGGCTGATGGGCAGTACC
TGCTCAACGGCAACCTGGCCATCTCTGCCATAGAGCAGGACATCTTGGTGAAGGGGACCATCTGAAGTACAGCGGCTCC
ATCGCCACCTGGAGCGCTGCAGAGCTTCGGGCCCTTGCCAGAGCCTCTGACAGTGCAGCTCCTGGCAGTCCCTGGCGA
GGTCTTCCCCCAAAGTCAAATACACCTTCTTTGTTCTTAATGACGTGGACTTTAGCATGCAGAGCAGCAAGAGAGAG
CAACCACCAACATCACCCAGCCGCTGCTCCACGCACAGTGGGTGCTGGGGGACTGGTCTGAGTGCTCTAGCACCTGCCGG
GCCGGCTGGCAGAGGCGAACTGTAGAGTGCAGGGACCCCTCCGGCCAGGCCTCTGCCACCTGCAACAAGGCTCTGAAACC
CGAGGATGCCAAGCCCTGCGAAAGCCAGCTGTCCCCCTGTGATTGAGGGGGCAGGGGCCAGTCTTGTGCTCCTGGACA
TGCGGTACTGAGGTGCAGACAAGGGTCTCCACTGTGGTGACTGGGTCCCTTGCCATATCAAGGCAGCACGGCCACCCA
GGCCTCCCATTGCCGAACCCCTCCAGTACTGCACAAATTCCTAAGGGGGAAGAGGAGGGGTATGGGGCGGCAGACCCT
ATCATCAACTGTCCAGTGGACTGGACCTTGCTCGGGTTCAAGTAGAGGGCATAGGTTAAAAGGTAAAAGTGCACTTATTG
TACCAGACAGGACGCCCGCAATTC

Fig. 1

2/39

RTKRFVSEARFVETLLVADASMAAFYGADLQNHILTLMSVAARIYKHPSIKNSINLMVVKVLIVEDEKKGPEVSDNGGLT
LRNFCNWQRRFNQPSDRHPEHYDTAILLTRQNFQCGQEGLCDTLGVADIGTICDPNKSCSVIEDEGLQAAHTLAHELGHVL
SMPHDDSKPCTRLFGPMGKHVMAPLFVHLNQTLPWSPCSAMYLTELLDGGHGDCLLDAPAAALPLPTGLPGRMALYQLD
QQCRQIFGPDFRHCNNTSAQDVCAQLWCHTDGAEPCHTKNGSLPWADGTPCGPGHLCSEGSCLPEEEVERPKPVVDGGW
APWGPWGECSRTC GGGVQFSHRECKDPEPQNGGRYCLGRRAKYQSCHEECPPDGKSFREQQCEKYNAYNYTMDGNLLQ
WVPKYAGVSPDRCKLFCRARGRSEFKVFEAKVIDGTLCGPETLAICVRGQCVKAGCDHVVDSEFWKLDKCGVCGGKGNCS
RKGSGSLTPTNYGYNDIVTIPAGATNIDVKQRSHPGVQNDGNYLALKTADGQYLLNGNLAIASIEQDILVKGTILKYSGS
IATLERLQSFRLPEPLTVQLLAVPGEVFPKVKYTFVPNDVDFSMQSSKERATTNITQPLLHAQWVLGDWSECSSTCG
AGWQRRTVECRDPGQASATCNKALKPEDAKPCESQLCPL.

Fig. 2

3/39

CCCCCCTCGAGGTGACGGTATCGATAAGCTTGATATCGAATTCGGGGCCCCACCCCGCCCCGTGAAACTTCTATAG
CAAATAGCAAACATCCAGCTAGACTCAGTCGCGCAGCCCCCTCCGGCGGGCAGCGCACTATGCGGCTCGAGTGGGCGTCC
TTGCTGCTGCTACTGCTGCTGCTGTGCGGCTCCTGCTGGCCCTGGCCGCTGACAACCCTGCCGCGCACCTGCCAGGA
TAAACAGGCAGCCTCGGGCTGCTGCAGCGGCTGCCAGCCGACCAGCGGCAGTGGGAGGAAACACAGGAGCGGGGCC
ATCTGCAACCCTTGCCAGGCAGCGCAGGAGCAGCGGGCTGGTGAGAATATAGACCAACTCTACTCTGGCGGTGGCAAA
GTGGGTACCTTGTCTACGCGGGCGGCCGAGGTTCTGTGGACCTGGAGAGGGATGACACAGTGGGTGCTGCTGGTGG
CATCGTTACTGCAGGAGGGCTGAGCGCATCCTCTGGCCACAGGGGTCAGTGTCTTACAGAGGCACTGTGGACGGCAGCC
CTCGATCCCTAGCTGTCTTTGACCTCTGTGGGGGTCTCGATGGCTTCTTCGAGTCAAGCATGCGCGCTACACTCTGAGG
CCGCTCTTGCGTGGGTCTGGGCAGAGTCCGAACGAGTTACGGGGATGGGTCTTACGCATCCTGCATGTCTACACCCG
CGAGGGCTTCAGCTTCGAGGCCCTGCCGCCACGCACCAGTTGCGAGACTCCAGCGTCCCGTCTGGGGCCCAAGAGAGCC
CCTCGGTGCACAGTAGTTCTAGGCGACGCACAGAACTGGCACCAGCTGCTGGACCATTAGCTTTCTCGCCAGCTGGG
AACCGGGACCTCAGACCTGGTGGAGGCGGAGGCGCGTTCCATCTCAGGGCCCGCCAGGTGGAGCTCCTCTTGGTGGC
TGACTCTTCCATGGCCAAGATGTATGGGCGGGCTGCAGCATTACCTGCTGACCCTGGCCTCTATTGCCAACC GGCTGT
ACAGTCATGCAAGCATCGAGAACCACATCCGCCTGGCCGTAGTGAAGTGGTGGTGTGACCGACAAGAGTCTGGAGGTG
AGCAAGAACCGGCCACGACCTCAAGAACTTTTGAAATGGCAGCACCAACACAACCAGCTAGGTGATGACCATGAGGA
GCACTACGATGCAGCCATCCTGTTACCAGAGAGGATTTATGTGGGCATCATTATGTGACACCCTGGGAATGGCAGACG
TTGGGACCATATGTTCTCCGAGCGCAGCTGCGCTGTGATTGAAGATGATGGCCTCCATGCAGCTTTCAGTGTGGCTCAC
GAAATTGGACATCTACTTGGCCTCTCTCAGCAGATTCCAAATCTGTGAAGAGAACTTTGGTTCTACAGAAGACAAGCG
TTTAATGTCTTCAATCCTTACCAGCATTGATGCATCCAAGCCCTGGTCCAAATGCACTTCAGCCACGATCACAGAATTC
TGGATGACGGTCATGGTAACTGTTTACTAGATGTACCACGGAAGCAGATTCTGGGCCCCGAGGAACCTCCAGGACAGACC
TATGATGCCACCCAGCAGTGCAACTTGACATTTGGGCTGAATACTCTGTGTGCCCTGGCATGGATGTCTGTGCACGGCT
GTGGTGTGCTGTGGTGCGCCAAGGCCAAATGGTGTGTCTGACCAAGAAGTTGCCTGCCGTGGAGGGCACTCCCTGTGGGA
AAGGAAGAATCTGCCTGCAAGGCAAATGTGTGGACAAAATAAGAAAAATATTACTCGACATCAAGCCATGGAAATTGG
GGGTCTGGGGCCCTGGGGTCAGTGTCTCGCTCTTGCGGGGAGGAGTACAGTTTGCCTACCGCCATTGCAATAACCC
CGCACCTCGAAACAGTGGCCGCTACTGCACAGGGAAGAGGGCCATATACCGTTCTGCAGTGTACACCTGCCACCTA
ACGGCAAATCTTCCGCCACGAGCAGTGTGAAGCAAAAATGGCTATCAGTCCGATGCAAAAGGAGTCAAAACATTTGTA
GAATGGGTTCCCAAATACGAGGTGTCTGCCGGCAGACGTGTGCAAGCTTACGTGCAGAGCTAAGGGCACTGGCTATTA
CGTGGTCTTTTCTCCAAAGGTTACAGATGGGACAGAATGTAGACCCTACAGCAACTCCGTGTGTGTCGAGGGAGGTGCG
TGAGAACGGGTGTGACGGCATCATCGGCTCAAAGTACAGTATGACAAGTGTGGAGTGTGTGGAGGGGATAACTCCAGT

Fig. 3A

4/39

TGTACAAAGATTATCGGAACCTTCAATAAAAAAGCAAGGGTTATACTGACGTTGTGAGGATCCCTGAAGGAGCAACCCA
CATAAAAGTCCGACAGTTCAAAGCCMAAGACCAGACTAGATTCAGTCTTACTTAGCCCTAAAGAAGAAAAGTGGCGAGT
ACCTTATCAACGGCAAGTACATGATCTCCACTTCAGAGACCATCATCGACATCAATGGTACCGTCATGAAGTACAGTGGG
TGGAGTCACAGAGATGATTTTTTACATGGGATGGGCTATTAGCCACAAAGGAAATTCTGATTGTGCAGATCCTTGCAAC
AGACCCAATAAGCATTAGACGTCCGTACAGCTTTTTTGTCCCAAGAAGACCACTCAAAAAGTGAATTCCTGCAGCC
CGGGGGATCCACTAGTTCTAGAGCGGCCG

Fig. 3B

MRLEWASLLLLLLLLCASCLALAADNPAAAPAQDKTRQPRAAAAAQPDRQWEETQERGLQPLARQRRSSGLVQNIQ
LYSGGKVGYL VYAGGRRFLDLERDDTVGAAGGIVTAGGLSASSGHRGHCFYRGTVDGSPRSLAVFDLCGGLDGFFAVK
HARYTLRPLL RGSWAESERVYGDGSSRILHVYTRREGFSFEALPPRTSCETPASPSGAQESPSVHSSRRRTAPQLLDH
SAFSPAGNAGPQTWRRRRRSISRARQVELLLVADSSMAKMYGRGLQHLLTLASIANRLYSHASIEHRLAVVKVVVL
TDKSLEVSKNAATTLKNFCKWQHQNQLGDDHEEHYDAAILFTREDLCGHSCDTLGMADVGTICSPERSCAVIEDGLH
AFTVAHEIGHLLGLSHDDSKFCEENFGSTEDKRLMSSILTSIDASKPWSKCTSATITEFLDDGHGNCLLDVPRKQILGP
EELPGQTYDATQQCNLTGPEYSVCPGMDVCAWLCAVVRQGMVCLTKKLPAVEGTPCGKGRICLQKCVDTKKKYYYS
TSSHGNGSWGPGWQCSCGGGVQFAYRHCNNPAPRNSGRYCTGKRAIYRSCSVIPCPNGKSFREHQCEAKNGYQSDA
KGVKTFVEWPKYAGVLPADVCKLTCRAKGTGYVVVSPKVTDTGTECRPYSNSVCVRGRCVRTGCDGIIGSKLQYDKCGV
CGGDNSSCTKIIGTFNKKSKGYTDVVRIPGATHIKVRQFKAXDQTRFTAYLALKKKTGEYLINGKYMISTSETIIDING
TVMNYSGWSHRDDFLHGMYSATKEILIVQILATDPTKALDVRYSFVPPKTTQKVNCSPPGDPLVLERP

Fig. 4

5/39

KIAA0605 Accession #: AB011177

```

cactggcggg gaaaatcccc tttttttttt tctctctctt tttttctttt tgagacggaa    60
tctcactctt tcacccagac tggagggcag cggcgagatc tgggtcact gcaacctcca    120
cctcccaggc tcaagcaatt ctctgcctc agccttccga gtagctggga ttacaggtgc    180
cggccaccac gccagctaa tttttgtatt tttagtagag acaggatitt accatgttgg    240
ccatgctggc ctcaaaactcc tgacctcgtg tgatcccccct gcttcagcct ctcaaaactgc    300
tgggattata ggcattgagcc actgcgcctg gccacaatc cctttctaaa ggcaggtggt    360
gtctccagca ccagggccat acggctgcaa cacccttaca agtgccgggt ctgccagaca    420
accacgacca actagtccca gataaccttg aggcctgggc actggctggg ccccgagggc    480
tcttcccaaa cgcgtacctg gtcatttga agaggatcgg agctggcctg gtggtgacag    540
tggccttggc tcttaggatg gatggcagat ggcaatgttc ctgctgggcc tgggttctgc    600
tggttctggc agttgtagct ggggacacag tgtcaaccgg gtccacggac aacagcccaa    660
catccaatac cctggagggg ggacccgacg ccacggcctt ctggtggggg gagtggacca    720
agtggacggc gttttccccc agttgcgggg gtggggtagc atcccaggag cggcactgcc    780
tgacgcagag gaggaagtcc gtcccgggcc ccgggaacag gacctgcacg ggcacgtcca    840
agcggtagca gctctgcaga gtgcaggagt gtccgcccga cgggaggagc ttccgcgagg    900
agcagtgctg ctcttcaac tcccacgtgt acaacggggc gacgcaccag tggaaagcctc    960
tgtaccggga tgactatgtc cacatctcca gcaaaccgtg tgacctgcac tgtaccaccg    1020
tggacggcca gggcagcttc atggtccccg cccgcgacgg cacatcctgc aagctcactg    1080
acctgcgagg ggtttgcgtg tctggaaaat gtgagcccat cggctgtgac ggggtgcttt    1140
tctccacca cacactggac aagtgtggca tctgccaggg ggacggtagc agctgcaccc    1200
acgtgacggg caactatcgc aaggggaaatg cccaccttgg ttacttctctg gtgaccaca    1260
tcccggctgg tgcccagac atccagattg tagagaggaa gaagtccgct gacgtgctag    1320
ctctgcaga tgaagctggc tactacttct tcaacggcaa ctacaagggt gacagcccca    1380
agaacttcaa catcgtctgc acggtgttca agtaccggcg gcccatggat gtctatgaga    1440
ccggaatcga gtacatcgtg gcacaggggc ccaccaacca gggcctgaat gtcatggtgt    1500
ggaaccagaa cggcaaaagc ccttccatca ccttcgagta cacgtgtctg cagccgccac    1560
acgagagccg cccccagccc atctactatg gcttctccga gacgctgag agccagggcc    1620
tggacggggc cgggctgatg ggcttcatcc cgcacaacgg ctccctctac ggcagggcct    1680
cctcagagcg gctgggcctg gacaaccggc gtctcgcca cccgggcctg gacatggagc    1740
tgggccccag ccagggccag gagaccaacg aggtgtccga gcaggccggc ggcggggcct    1800
gcgagggggc ccccaggggc aagggtctcc gagaccgcaa cgtcacgggg acicctctca    1860
ccggggacaa ggatgacgaa gaggttgaca ccaacttcgc ctcccaggag ttcttctcgg    1920
ctaacgcat ctctgaccag ctgctgggag caggtcttga cttgaaggac ttcacctca    1980
atgagactgt gaacgacatc ttgtcacagg gcgccccaa gacgtccctg gccgagagct    2040
tcttcgtgga ttatgaggag aacgaggggg ctggccctta cctgtcctaac ggttcttacc    2100
tggagctgag cagcgacagc gttgccaaca gctcctccga ggccccattc cccaacgtta    2160
gcaccagcct gctcactctg gccgggaaca ggactcaca ggccaggacc aggcccaagg    2220
cgcgcaagca aggctgaggt cccgcggaca tgtaccggtg gaagctctcg tcccagagc    2280
cctgcagtgc cactgcacc acaggggtca tgtctgcgta cgccatgtgt gtccgctatg    2340
atggcgctga ggtgatgac agctactgtg acgcccgtac ccgtcccag cctgtccacg    2400
agtctgcgc tgggaggagg tgccagccca ggtgggagac gacgagctgg agcagtggt    2460

```

Fig. 5A

6/39

cgcgccctg cggagagggc taccagtcc gcgtcgtgc ctgctggaag atgctctcgc 2520
 ccggcttcga cagctccgtg tacagcgacc tgtcgagggc agccgagggc gtgcggccc 2580
 aggaacgcaa gacctgccg aaccccgct gcgggcccc gtggagatg tcggagtgt 2640
 ccgagtgac tgccaagtgt ggggagcgca gtgtgtgac caggacatc cgtcgtcgg 2700
 aggatgaga gctgtgtgac ccaacacca gccctgtagg ggagaagaac tgcacgggc 2760
 cgccctgtga ccggcagtgg accgtctccg actggggacc gtgcagtga agctcgggc 2820
 aaggccgcac catcaggcac gtgtactga agaccagcga cggacggga gtacctagt 2880
 cccagtcca gatggagacc aagcctctgg ccatccacc ctgtggggac aaaaactgtc 2940
 ccgcccactg gctggccag gactgggagc ggtgcaaac cacctgcgg cgcggggtca 3000
 agaagcggct ggtgctctc atggagctgg ccaacggga gccgcagac cgagtgggc 3060
 ccgagtcgg gctcgccaag aagcctccc aggagagcac gtgtttcag agccctgct 3120
 tcaagtggta caccagcccc tggcagagt gcaccaagac ctgcggggtg ggcgtgagg 3180
 tgcgagcgt caagtgtac caggggacc acatcgtccg tgggtgcgat ccgttggta 3240
 agcccggtg cagacaggcc tgtgatctg agccctgcc cagggagccc ccagatgaca 3300
 gctgccagga ccagccaggc accaactgt cctggccat caaagtgaac ctctgcggc 3360
 actgtacta cagcaaggcg tctgcccgt cctgcaggc cccccactc taggccggc 3420
 agctgcagc ccttcagat gaagaccaag cgccctcct gggctgctg cagctcttg 3480
 ggcccccaca gacccccc ctcggggca cgctggccta agagacgtg cactgagcct 3540
 cgctgtcga gaggggactt cccacggccc gtggacctt gtgctcctg ggcagagcct 3600
 ccggaccca gtggcctccc ccagacagag ccaacctgc cgtgggaacc tgcctgtt 3660
 cctgcgtga tctgtgtt gtggctcca cccccagc cccagcagc cccagccga 3720
 gggggccagg gccacagcc agcgttgag gtgtcttgc ccgggccgt agccacgcc 3780
 ctctctggg ggcaggcct tctgaaggaa acttcagc gagcccaac tggggggg 3840
 ccttctccc tcagaggcca tgggtgaga ggggtcagg cagccaagga gggcaggcg 3900
 tctcctct tatggagcc ctcctatga gctctctc cgccgactt tctaccccg 3960
 gcagaggcg ttgccacg gacgttgg gatggacct gggcccgcc cctgcagtca 4020
 gcgtcagtgc tcatctacgt taataaagt gtcctatta tggcggc 4067

Fig. 5B

MDGRWQCSCWAWFLVLAVVAGDTVSTGSDNSPTNSLEGDTAFWGEWKWTFASRSCGGVTSQERHCLQRRKSVPGNRTCTGTSKRYQ
 LCRVQECPPDGRSFREEQCVSFNSHVYNGRTHQWKPLYDDYVHISKPCDLHCTTVDGQRQLMVPARDGTSCKLTDLRGVCVSGKCEPIGCDGLFS
 THLDKCGICQGDGSSCTHTVGNRYKGNALGYSLVTHIPAGARDIQIVERKKSADVLALADEAGYFFNGNYKVDSPKNFNIAGTVVKYRRPMOYVE
 TGI EYVAQGPTNOGLNVMVWQNGKSPSITFEYLLQPPHESRPQPIYYGFSESAESQGLDAGLMGFI PHNGSLYGOASSERLGLDNRLFHHPGLD
 MELGPSQGOETNEVCEQAGGGACEGPPRGKGFDRNVTGTPLTGDKDDEEVDTHFASQEFFSANAISDQLLGAGSDLKDFTLNETVNSIFAQAPRSS
 LAESFFVDYEENEGAGPYLLNGSYLELSSDRVANSSSEAPFPNVSTSLLSAGNRTHKARTRPKARKQGVSPADMYRWKLSSEPCSATCTTGVM SAY
 AMCVRYDGEVDDSYCDALTRPEPVHEFCAGRECQPRWETSSWSECSRTCGEGYQFRVVRWKM LSPGFDSYVSDLCEAAEAVRPEERKTCRNPACG
 PQWEMSEWSECTAKCGERSVVTDRIRCEDEKLCDPNTRPVGEKNCTGPPCDRQWTVSDWGPCSGSCGQGRIRHYVCKTSDGRVVPESQCMETKPL
 AIHPGDKNCPAHWAQDWERCNTTCGRGVKKRLVLCMELANGKQPTRSGPEGLAKKPEESTCFERPCFKWYTSWSECTKTCGVGVVRMDVKCYQ
 GTDIVRGCDPLVKPVGRQACDLQPCPTEPPDDSCDQPGTNCALAIKVNLCGHWYYSKACCRSCRPPHS (951 amino acids)

Fig. 6

SUBSTITUTE SHEET (RULE 26)

7/39

DNA sequence of metalloproteinase gene (KIAA0366) Accession #: AB002364

```

gtcactttgg ttgatagcag ccgctcrggt agaggtagg acttcagctg atggacaagc 60
tggtaatgaa gaaatggigc aaatagattt accaataaag agatatagag agtatgagct 120
ggtagactcca gtcagacaaa atctagaagg acgctatctc tcccatactc tttctgcgag 180
tcacaaaagg aggtcagcga gggacgtgtc ttccaaccct gagcagttgt tctttaacat 240
cacggcattt ggaaaagatt ttcactgtcg actaaagccc aacactcaac tagtagctcc 300
tggggctggt gtggagtggc atgagacatc tctggtgcct gggaatataa ccgatcccat 360
taacaaccat caaccaggaa gtgtacgta tagaatccgg aaaacagagc ctttgagac 420
taactgtgct tatgttgggt acatcgtgga cattccagga acctctgttg ccatcagcaa 480
ctgtgatggt ctggctggaa tgataaaaag tgataatgaa gagtatttca ttgaaccctt 540
ggaaagaggt aaacagatgg aggaagaaaa aggaaggatt catgttgtct acaagagatc 600
agctgtagaa caggctccca tagacatgtc caaagacttc cactacagag agtcggacct 660
ggaaaggcctt gatgatctag gtactgttta tggaacatc caccagcagc tgaatgaaac 720
aatgagacgc cgcagacacg cgggagaaaa cgattacaat atcgaggtag tgctgggagt 780
ggatgactct gtggtccgtt tccatggcaa agagcacgtc caaaactacc tcctgacctt 840
aatgaacatt gtgaatgaaa ttaccatga tgagtccctc ggagtgcata taaatgtggt 900
cctggtgcgc atgataatgc tgggatatgc aaagtccatc agcctcatag aaaggggaaa 960
cccattccaga agcttgagaa atgtgtgtcg ctgggcgtcc caacagcaaa gatctgatct 1020
caaccactct gaacaccatg accatgcaat tttttaacc aggcagact ttggacctgc 1080
tggaatgcaa ggatatgtct cagtcaccgg catgtgtcat ccagtgaaga gttgtaccct 1140
gaatcatgag gatggttttt catctgtttt tgtagtagcc catgaaacgg gccatgtgtt 1200
gggaatggag catgatggac aaggcaacag gtgtggtgat gagactgcta tgggaagtgt 1260
catggctccc ttgttacaag cagcattcca tcgttaccac tggccccgat gcagtgttca 1320
agaactgaaa agatatatcc attctatga ctgtctcctt gatgacctt ttgatcatga 1380
ttggcctaaa ctcccagaac ttcttgaar caattattct atggatgagc aatgtcgttt 1440
tgattttggt gttggtcata aaatgtgcac cgcgttccga accttgacc catgtaaca 1500
gctgtggtgt agccatcctg ataaccctca cttttgtaag actaaaaagg gacctccact 1560
tgatgggact gaatgtgctg ctggaatatg gtgtataag ggtcattgca tgtggaagaa 1620
tgctaatacag caaaaacaag atggcaattg ggggtcatgg actaaattg gctcctgttc 1680
tcggacatgt ggaactgggt ttcgtttcag aacacgccag tgcaataatc ccatgcccat 1740
caatggtggt caggattgtc ctggtgttaa ttttgagtac cagctttgta acacagaaga 1800
atgccaaaaa cactttgagg acttcagagc acagcagtg cagcagcgaa actcccactt 1860
tgaataccag aataccaaac accactggtt gccatatgaa catcctgacc ccaagaaaag 1920
atgccacctt tactgtcagt ccaaggagac tggagatgtt gcttacatga aacaactggt 1980
gcatgatgga acgactgtt cttacaaaga tccatatagc atatgtgtgc gaggagagt 2040
tgtgaaagt 2100
ctgtggaaga gataattccc actgccgaac cgtgaagggt acattacca gaactcccag 2160
gaagcttggg taccttaaga tggttgatat accccttggg gctagacatg tgtaatcca 2220
agaagacgag gcttctctc atattctgc tattaagaac caggctacag gccattatat 2280
tttaaatggc aaaggggagg aagccaagtc gcggacctc atagatctg gtgtggagt 2340
ggattataac attgaagatg acattgaaag tcttcacacc gatggacctt tacatgatcc 2400
tggtattgtt ttgattatac ctcaagaaaa tgataccgc tctagctga catataagta 2460
catcatccat gaagactctg tacctacaat caacagcaac aatgtcatcc aggaagaatt 2520

```

Fig. 7A

8/39

```

agatactttt gagtgggctt tgaagagctg gtctcaggtt tccaaaccct gtggaggagg 2580
tttccagtac actaaatag gatgccgtag gaaaagtgat aataaaatgg tccatcgag 2640
cttcgtgag gccacaaaa agccgaaacc tattagacga atgtgcaata ttcaagagt 2700
tacacatcca ctctgggtag cagaagaatg ggaacactgc accaaaacct gtggaagttc 2760
tggtatcag cttcgcactg tacgtgcctt tcagccactc ctgatggca ccaaccgctc 2820
tgtgcacagc aaatactgca tgggtgaccg tcccgagagc cgccggccct gtaacagagt 2880
gcccgcctt gcacagtggg aaacaggacc ctggagtga gtttcagtga cctgcggtga 2940
aggaacggag gtgaggcagg tccctctcag gcctggggac cactgtgatg gtgaaaagcc 3000
tgagtcggc agagcctgtc aactgcctcc ttgtaatgat gaaccatgtt tgggagacaa 3060
gtccatattc tgcaaatgg aagtgttggc acgatactgc tccataccag gtataacaa 3120
gttatgttg gagtcctgca gcaagcgag tagcaccctg ccaccacat accttctaga 3180
agctgctgaa actcatgag atgtcatctc taaccctagt gacctcccta gatctctagt 3240
gatgcctaca tctttggtc ctatcattc agagacccct gcaagaaga tgtctttgag 3300
tagcatctct tcagtgggag gtccaaatgc atatgctgct ttcaggccaa acagtaaacc 3360
tgatggtgct aatttacgc agaggagtgc tcagcaagca ggaagtaaga ctgtgagact 3420
ggtcaccgta ccatccccc caccaccaa gaggggtccac ccagttcag cttcacaaat 3480
ggctgctgct tcttctttg cagccagtga ttcaataggt gcttctctc aggcaagaac 3540
ctcaagaaa gatggaaga tcattgacaa cagacgtccg acaagatcat ccacctaga 3600
aagatgagaa agtgaaccaa aaaggctaga aaccagagga aaacctggac aacctctctc 3660
ttcccatggt gcatagtctt gtttaagtgt gaaatctcta tagatcgta gctcatttta 3720
tctgtaattg gaagaacaga aagtgtggc tcactttcta gtgtcttca tctcctttt 3780
gttctgcatt gactcattta ccagaattca ttggaagaaa tcaccaagaa ttattacaaa 3840
agaaaaatat gttgctaaga ttgtgttgt cgctctctga agcagaaaag ggactggaac 3900
caattgtgca tatcagctga cttttgttt gttttagaaa agttacagta aaaattaaaa 3960
agagatacca atggtttaca ctttaacaag aaattttgga tatggaacaa agaattctta 4020
gactgttatt cctatttatc tatattagaa atattgtatg agcaaattg cagctgttgt 4080
gtaaatctg tatatgcaa aatcagtat taatttaaga gatgtgttct caaatgattg 4140
tttactatat tacatttctg gatgttctag gtgcctgtcg ttgagtattg ccttgtttga 4200
cattctatag gtttaatttc aaagcagagt attacaaaag agaagttaga attacagta 4260
ctgacaatat aaagggtttt gttgaatcaa caatgtgata cgtaaattat agaaaaagaa 4320
aagaaacaca aaagctatag atatacagat atcagcttac ctattgcctt ctatacttat 4380
aatttaaagg attggtgtct tagtacactt gtggtcacag ggaatcaacga atagtaata 4440
atgaactcgt gcaagacaaa actgaaaccc tctttccagg acctcagtag gcaccgttga 4500
gggtgccttt gtttttgtgt gtgtgtgttc ttttttaatt ttcgatttgt tgacagatac 4560
aaacagttat actcaatgta ctgtaataat cgcaaggaa aaagttttg gataacttat 4620
ttgtatgttg gtactgaga aaaatatcat cagtctagaa ttgatattg agtatagtag 4680
agctttggg ctttgaaggc aggttcaaga aagcatatgt cgtagggtga gatatttatt 4740
ttccatagtg ttcatgttca aatgttcaca accacaatgc atctgactgc aataatgtgc 4800
taataattta tgtcagtagt cacttgctc acagcaaagc cagaaatgct ctctccaggg 4860
agtagatgta aagtacttgt acatagaatt cagaactgaa gatatttatt aaaagttgat 4920
tttttttct ttagatgatt tttatgtact aaatatttac actaatatca attacatatt 4980
ttggtaaact agagagacat aattagagat gcagtctttg ttctgtgcat agagaccttt 5040
aagcaaaacta ctacagccaa ctcaaaagct aaaactgaac aaatttgatg ttatgcaaac 5100
atcttgcat tttagtagtt gatattaagt tgatgacttg tttcccttca aggaacatt 5160

```

Fig. 7B

9/39

aaattgtag gactcagcta gctgttcaat gaaattgtga attagaaaca tttttaaaag 5220
 tttttgaaag agataagtc atcatgaatt acatgtacat gagaggagat agtgatatca 5280
 gcataatgat tttaggtca gtaccigagc tgtctaaaaa tatattatac aaactaaaat 5340
 gtagatgaat taacctctca aagcacagaa tgtgcaagaa cttttgcatt ttaatcgtg 5400
 taaactaaca gcttaacta ttgactctat acctctaaag aattgctgct actttgtgca 5460
 agaactttga aggtcaaat aggcaaatc cagatagtaa aacaatccct aagccitaag 5520
 tcttttttt ttcttaaaaa ttcccataga ataaaattct ctctagttta cttgtgtgtg 5580
 catacatctc atccacaggg gaagataaag atggtcacac aaacagtttc cataaagatg 5640
 tacatatcta ttatacttct gacctttggg ctttcttttc tactaagcta aaaattcctt 5700
 tttatcaaag tgcacaciac tgatgctgtt tgtgtactg agagcacgta ccaataaaaa 5760
 tgtaacaaa atat 5774

Fig. 7C

1 80
 slwliaaalvevrt sadgag neemvqidlpikryeyeivtpvstnlegrylshtlsashkkr sardvssnpeqlffni
 tafgkdfhlrlkpnqlvapgavvewhetslvpgnitdpinnhqpsatyirkteplqtncayvgdivdipgtsvaisn
 cdglagmiks dneeyfieplergkqmeekgrihvvykrsaveqapidmskdfhyresdlegldlgtvygnihqqlnet
 mrrrrhagendynievllyvddsvvrfhgkehvnqylltlnmivneyhdeslgvhinvvlmimlgyaksisliern
 psrslenvcrwasqqrsdlnhsehdhaifltrqdfgpagmqyapvtgmchpvrsc lnhedgfssa fvvahetghvl
 gmehdgggnrcgdetamgs vmaplvqaafrhyhwsrscgqelkryihsydc llddpfdhdwpklpelpginysmdeqcrf
 dfvgvykmctaftrtdpckqlwchshpndpyfcktkkgppldgtecaagkwcykghcmwknanqqkdgnwgswtkfgscs
 rtcgtgvrfrtrqcnmpingggdcpgvnfeyqlcnteecqkhfedfraqqcqrnshfeyqntkhhwlp yehdpdkkr
 chlycasketgdvaymkqlvhdgthcsykdpysicvrgecvkvgcdkeigsnkvedkcgvcggnshcrtvkgtftrtp
 klgyikmf dipgarhvlqedea philaikenqatghylngkgeaksrtfidlgvewdynieddieslhtdgp lhd
 vivliipqendtrssltkyi ihedsvptinsnnviqueeldtfewalkswsqvskpcgggfytkygcrrksdnkmvns
 fceankkpkpirmcniqecthplwaeewehctktcgssgyqlrtvrc lqplldgtnrsvhskycmgdrpesrrpcnrv
 pcpaqwktpwsecsvtcgegtevrqlcragdhcdgekpesvracqlppcndepclgdksifcmevlarycsipgynk
 lccescskrsstlpppylleaethddvisnpsdlprslvmptslvpyhsetpakkmslssissvggnayaafrpnskp
 dganlqrssaqqagsktvrlvtvpsspptkrvhlssasqmaasffaasdsigassqartskkdgkiidnrrptrsstle
 r (1.201)

Fig. 8

10/39

GGAATTCGCGGCCGCTCGACGTCAATACCAACTCCGAGCACACGGCCGTCATCAGCCTCTGCTCAGGAATGCTGGGCAC
ATTCGGTCTCATGATGGGGATTATTTTATTGAACCACTACAGTCTATGGATGAACAAGAAGATGAAGAGGAACAAAACA
AACCACATCATTTATAGGCGCAGCGCCCCCAGAGAGAGCCCTCAACAGGAAGGCATGCATGTGACACCTCAGAACAC
AAAAATAGGCACAGTAAAGACAAGAAGAAAACAGAGCAAGAAAATGGGGAGAAAGGATTAACTGGCTGGTGACGTAGC
AGCATTAAACAGCGGCTTAGCAACAGAGGCATTTTCTGCTTATGGTAATAAGACGGACAACACAAGAGAAAAGAGGCC
ACAGAAGGACAAAACGTTTTTATCCTATCCACGGTTTGTAGAAGTCTTGGTGGTGGCAGACAACAGAATGGTTTCATAC
CATGGAGAAAACCTTCAACACTATATTTTAACTTTAATGTCAATTGATGGGCCCTCCATATCTTTAATGCTCAGACAAC
ATAAAAAACCTTTGCCAGTGGCAGCATTGAAGAAGTCCAGGTGGAATCCATCATGATACTGCTGTTCTCTTAACAA
GACAGGATATCTGCAGAGCTCAGACAAATGTGATACCTTAGGCCTGGCTGAAGTGGGAACCATTTGTGATCCCTATAGA
AGCTGTTCTATTAGTGAAGATAGTGGATTGAGTACAGCTTTACGATCGCCATGAGCTGGGCCATGTGTTTAACATGCC
TCATGATGACAACAACAAATGTAAAGAAGAAGGAGTTAAGAGTCCCAGCATGTCATGGCTCCAACACTGAAGTCTTACA
CCAAACCTGGATGTGGTCAAAGTGTAGTCGAAAATATATCACTGAGTTTTTAGACACTGGTTATGGCGAGTGTGCTT
AACGAACCTGAATCCAGACCTACCTTTGCCTGTCCAAGTCCAGGCATCCTTTACAACGTGAATAAACAATGTGAATT
GATTTTTGGACCAGTTCTCAGGTGTGCCATATATGATGCAGTGCAGACGGCTCTGGTGCAATAACGTCAATGGAGTAC
ACAAAGGCTGCCGACTCAGCACACACCCTGGGCCGATGGGACGGAGTGCAGCCTGGAAAGCACTGCAAGTATGGATTT
TGTGTTCCCAAAGAAATGGATGTCCCGTGACAGATGGATCCTGGGGAAGTTGGAGTCCCTTTGGAACCTGCTCCAGAAC
ATGTGGAGGGGGCATCAAAACAGCCATTCGAGAGTGCAACAGACCAGAACCAAAAATGGTGGAAAATACTGTGTAGGAC
GTAGAATGAAATTTAAGTCTGCAACACGGAGCCATGTCTCAAGCAGAAGCGAGACTTCCGAGATGAACAGTGTGCTCAC
TTTGACGGGAAGCATTTTAACATCAACGGTCTGCTTCCCAATGTGCGCTGGGTCCCTAAATACAGTGGAAATCTGATGAA
GGACCGGTGCAAGTTGTTCTGCAGAGTGGCAGGGAACACAGCCTACTATCAGCTTCGAGACAGAGTGATAGATGGAACTC
CTTGTGGCCAGGACACAAATGATATCTGTGTCCAGGGCCTTTGCCGGCAAGCTGGATGCGATCATGTTTTAACTCAAAA
GCCCCGAGAGATAAATGTGGGGTTTGTGGTGGCGATAATCTTCATGCAAAACAGTGGCAGGAACATTTAATACAGTACA
TTATGGTTACAATACTGTGGTCCGAATTCAGCTGGTGTACCAATATTGATGTGCGGCAGCACAGTTTCTCAGGGGAAA
CAGACGATGACAACCTACTTAGCTTTATCAAGCAGTAAAGGTGAATTCTTGCTAAATGGAACTTTGTTGTCACAATGGCC
AAAAGGGAAATTCGATTGGGAATGCTGTGGTAGAGTACAGTGGGTCCGAGACTGCCGTAGAAAGAATTAACCAACAGA
TCGATTGAGCAAGAACTTTTGCTTCAGGTTTTGTGCGTGGGAAAGTTGTACAACCCGATGTACGCTATTCTTCAATA
TTCCAATTGAAGATAAACCTCAGCAGTTTTACTGGAACAGTCATGGCCATGGCAAGCATGCAGTAAACCTGCCAAGGG
GAACGGAAACGAAAACCTGTTTGCACCAGGGAATCTGATCAGCTTACTGTTTCTGATCAAAGATGCGATCGGCTGCCCCA
GCCTGGACACATTACTGAACCTGTGGTACAGACTGTGACCTGAGGTGGCATGTTGCCAGCAGGAGTGAATGTAGTGCCC

Fig. 9A

11/39

AGTGTGGCTTGGGTTACCGCACATTGGACATCTACTGTGCCAAATATAGCAGGCTGGATGGGAAGACTGAGAAGGTTGAT
GATGGTTTTTGCAGCAGCCATCCCAAACCAAGCAACCGTGAAAAATGCTCAGGGGAATGTAACACGGGTGGCTGGCGCTA
TTCTGCCTGGACTGAATGTTCAAAAAGCTGTGACGGTGGGACCCAGAGGAGAAGGGCTATTTGTGTCAATACCCGAAATG
ATGTACTGGATGACAGCAAATGCACACATCAAGAGAAAGTTACCATTGAGAGGTGCAGTGAGTTCCTTGTCACAGTGG
AAATCTGGAGACTGGTCAGAGTGCTTGGTCACCTGTGGAAAAGGGCATAAGCACCGCCAGGTCTGGTGTGAGTTTGGTGA
AGATCGATTAAATGATAGAATGTGTGACCCAGAGGTGACGCGGCCGGAATTCGCGCGATACTGACGGGCTCCAGGAGT
CGTCGCCACCAATCCCATATGGAAACCGTCGATATTCAGCCATGTGCCTTCAAGCCGAATTCAG

Fig. 9B

GIRGRVDVNTNSEHTAVISLCSGMLGTFRSHDGDYFIEPLQSMDEQEDEEEQNKPHEIYRRSAPQREPSTGRHACDTSEH
KNRHSKDKKKTRARKWGERINLAGDVAALNSGLATEAFSAYGNKTDNTRKTRHRTRKFLSYPRFVEVLVADNRMVSY
HGENLQHYILTLMSIDGPSISFNAQTTLKNLCQWQHSKNSPGGIHHDTAVLLTRODICRAHDKCDTLGLAELGTICDPYR
SCSISEDGLSTAFTIAHELGHVFNMPHDDNNKCKEEGVKSPQHVMAPTLNFYTNPMMWSKCSRKYITEFLDTGYGECCL
NEPESRPYPLPVQLPGILYNVNKQCELI FGPGSQVCPYMMQCRRLWCNNVNGVHKGCRTOHTPWADGTECEPGKHCKYGF
CVPKEMDVPVTDGSGWSWSPFGTCSRTCGGGIKTAIRECNRPKNGGKYCVGRRMKFKSCNTEPCLKQKRDFRDEQCAH
FDGKHFNINGLLPNVRWVPKYSGILMKDRCKLFCRVAGNTAYYQLRDRVIDGTPCGQDTNDICVQGLCRQAGCDHVLNSK
ARRDKCGVCGGDNSSCKTVAGTFNTVHYGYNTVVRI PAGATNIDVRQHSFSGETDDDNYLALSSSKGEFLNGNFVVTMA
KREIRIGNAVVEYSGSETAVERINSTDRIEQELLLQVLSVGKLYNPVRYSFNPIEDKPQQFYWN SHGPWQACSKPCQG
ERKRKL VCTRESQQLTVSDQRCDRLPQPGHIT EPCGTDCDLRWHVASRSECSAQCGLGVRTLDIYCAKYSRLDGKTEKVD
DGFCSHPKPSNREKCSGECNTGGWRYSAWTECSKSCDGGTQRRRAICVNTRNDVLD DSKCTHQEKVTIQRCEFP CPQW
KSGDWSECLVTCGKGHHRQVWCQFGEDRLNDRMCDPEVDAAANSADTGLQESSPIPIWKPSIFSHVPSSRIP

Fig. 10

12/39

cacatatgcacgagagagacagaggagaaagagacagagacaaaggcacagcggaagaaggcagagacagggcaggcac
agaagcggcccagacagagtcctacagagggagagggccagagaagctgcagaagacacaggcagggagagacaaagatcc
aggaaaggagggtcaggaggagagtttgagaagccagacccctgggcacctctccaagcccaaggactaagttttct
ccatttcctttaacgggtccicagcccttctgaaaactttgcctctgaccttggcaggagtccaagccccaggctacaga
gaggagctttccaaagctaggggtgtggaggacttggccttagacggcctcagtcctcccagctgcagtaccagtgcc
atgtcccagacaggctcgcacccgggaggggcttggcagggcgctggctgtggggagcccaacctgcctcctgtctccc
cattgtgccgctctcctgggtgggtgtggctgcttctgctactgctggcctctctcctgccctcagccccgggtggccagcc
ccctccccgggaggaggagatcgtgttccagagaagctcaacggcagcgtcctgcctggctcgggcacccctgccagg
ctgttgtgccgcttgcaggcctttggggagacgctgctactagagctggagcaggactccggtgtgcaggctcaggggct
gacagtgcagtacctgggagggcgctgagctgctgggtggagcagagcctggcacctacctgactggcaccatcaatg
gagatccggagtcggtggcatctctgactgggatgggggagccctgttaggcgtgttaaatatcggggggctgaactc
cacctccagccccggaggaggcaccctaaactcgtcgggggacctggggctcacatcctacgccgaagagtcctgc
cagcggtaaggctcccatgtgcaacgtcaaggctcctcttgaagccccagccccagaccggaagagccaagcgtttg
cttactgagtagatttgtggagacactggtgggtggcagatgacaagatggcgcattccacggtgcggggctaaagcgc
tacctgctaacagtgtatggcagcagcagccaaggcctcaagcaccgaagcatccgaatcctgtcagcttgggtggac
tcggctagtgtatcctggggtcaggcgaggagggggcccaagtggggccagtgctgccagaccctgcgcagcttctgtg
cctggcagcgggctcaacacccctgaggactcggaccctgaccactttgacacagccattctgtttaccgctcaggac
ctgtgtggagtctccacttgcgacacgctgggtatggctgatgtgggcaccgtctgtgacccggctcggagctgtgcat
tgtggaggatgatgggctccagtcagccttactgctgctcatgaactgggtcatgtcttcaacatgctccatgacaact
ccaagccatgcatcagtttgaatgggcctttgagcacctctcgccatgtcatggcccctgtgatggctcatgtggatcct
gaggagccctgggtccccctgcagtggcgcttcatcactgacttcctggacaatggctatgggactgtctcttagacaa
accagaggctccattgcatctgcctgtgactttccctggcaaggactatgatgctgaccgccagtgccagctgacctc
ggcccgactcacgccattgtccacagctgccgccctgtgctgccctctggtgctctggccacctcaatggccatgcc
atgtgccagacaaactcgcctgggcccagtgccacacctgcggggccgcagggcctgcatgggtggtcgtgcct
ccacatggaccagctccaggacttcaatatccacaggtgggtgggtccttggggaccatggggtgactgctctc
ggacctgtgggggtggtgtccagtctcctcccagactgcacgaggcctgtcccccggaatggtggcaagtactgtgag
ggccgctgacctcctcctcctgcaacactgaggactgccaactggctcagccctgaccttccgcgaggagcagtg
tgctgcctacaaccaccgcaccgacctctcaagagcttccagggccatggactgggttctcgtacacaggcgtgg
ccccccaggaccagtgcacaaactcacctgccaggccgggactgggtactactatgtgctggagccacgggtggtgat

Fig. 11A

13/39

gggaccccctgttccccggacagctcctcggtctgtgtccagggccgatgcatccatgctggctgtgatcgcatcattgg
ctccaagaagaagittgacaagtgcattggtgtgcggaggggacggttctggttgacgaagcagtcaggctccttcagga
aattcaggtacggatacaacaatgtgtgcactatccccgcggggccaccacattcttgcggcagcagggaaaccct
ggccaccggagcatctacttggccctgaagctgccagatggctcctatgccctcaatggtgaatacacgctgatgccctc
ccccacagatgtggtactgcctggggcagtcagcttgctacagcggggccactgcagcctcagagacactgtcaggcc
atggggcactggcccagcctttgacactgcaagtcctagtggctggcaacccccaggacacacgcctccgatacagcttc
ttcgtgccccggcgaccccttcaacgccacgccccactccccaggactggctgcaccgaagagcacagattctggagat
ccttcggcgggcggccctggggcggcaggaaataacctcactatcccggctgccctttctgggcaccggggcctcggactt
agctgggagaaagagagagcttctgttgcctcatgctaagactcagtggggaggggctgtggcgctgagacctgcc
ctcctctctgccctaagcgcaggctggccctgccctggttctgccctgggaggcagtgatgggttagtgatggaag
gggctgacagacagccctccatctaaactgccccctgcctgcgggtcacaggaggaggagggaaggcaggaggggcc
tgggccccagttgtatttatttagtatttattcacttttatttagcaccagggaagggaacaaggactagggtcctggg
aacctgaccctgacccctcatagccctcaccctggggctaggaaatccagggtggtggtgataggatataagtgggtgt
gtatgcgtgtgtgtgtgtgtgaaatgtgtgtgtgcttatgtatgaggtacaacctgttctgcttctcctctctgaa
ttttatttttgggaaaagaaaagtcagggtagggtgggccttcagggaagtgggattatcttttttttttttcttt
ctttctttcttttttttttttgagacagaatctcgctctgtcgccaggctggagtgaatggcacaatctcggtcact
gcatcctccgctcccgggttcaagtgattctcatgcctcagcctcctgagtagctgggattacaggctcctgccaccac
ggccagctaattttgtttgtttgtttggagacagagtcctcgctattgtcaccagggtggaatgatttcagctcact
gcaaccttcgccacctgggttccagcaattctcctgcctcagcctcccagtagctgagattataggcacctaccaccac
ggccggctaattttgtatttttagtagagacggggttccaccatggtggccaggctggtctcgaactcctgacctagg
tgatccactcgctcatctcccaaagtgtgggattacaggcgtgagccaccgtgcctggccacgcccactaatttt
gtatttttagtagagacaggggttccaccatggtggccaggctgctctgaactcctgacctcaggtaatcgacctgcctc
ggcctcccaaagtgtgggattacagggtgtgagccaccacgggtacataatttttaattgaattctactatttatg
tgatccttttggagtcagacagatgtggtgcatcctaactccatgtctctgagcattagatttctcatttgccaataat
aatacctcccttagaagttgtgtgaggattaaataatgtaaataaagaactagcataac

Fig. 11B

14/39

MSQTGSHPGRLAGRWLWGAQPCLLLPIVPLSWLVLLLLLLASLLPSARLASPLPREEEIVFPEKLNQSVLPGSGTPAR
LLCRLQAFGETLLELEQDSGVQVEGLTVQYLGQAPELLGGAEPGYLTGTINGDPESVASLHWDGGALLGVLYRGAEL
HLQPLEGGTPNSAGGPGAHILRRKSPASGGQPMC NVKAPLGSPSPRRRAKRFASLSRFVETLVVADDKMAAFHGAGLKR
YLLTVMAAAAKAFKHPSIRNPVSLVVTRLVILGSGEEGPVGPSAAQTLRSFCAWQRLNTPEDSDPDHFDTAILFTRQD
LCGVSTCDTLGMADVGTVCDPARSCAIVEDDGLQSAFTAAHELGHVFNMLHDNSKPCISLNGPLSTSRHVMAFVMAHVP
EEPWSPCSARFITDFLDNGYGHCLLDKPEAPLHLPVTFPGKDYDADRQCQLTFGPDSRHCPQLPPPCAALWCSGHLNGHA
MCQTKHSPWADGTPCGPAQACMGGRLHMDQLQDFNIPQAGGWGPWGPWGDCSRTC GGGVQFSSRDCTRPVPRNGGKYCE
GRRTRFRSCNTEDCPTGSALTFREEQCAAYNHRTDLFKSFPGMDWVPRYTGVAPQDQCKLTCQARALGYYYVLEPRVVD
GTPCSPDSSSVCVQGRCIHAGCDRIIGSKKKFDKCMVCGDGGSGCSKQSGSFRKFRYGYNVVTIPAGATHILVRQQGNP
GHRSIYLALKLPDGSYALNGEYTLMPSPTDVVLPGAVSLRYSGATAAETLSGHGPLAQPLTLQVLVAGNPQDTRLRYSF
FVPRPTPSTPRPTQDWLHRAQILEILRRRPWAGRK

Fig. 12

15/39

Rat ADAMTS 5 DNA

ACTCACTATA GGGCTCGAGC GGCCGCCCGG GCAGGTCAGA GGCTCACTGG CAGCTCTCTA	60
GACCTGCGAC GCTGCTTCTA TTCCGGGTAT GTGAACGCGG AGCCAGACTC CTTTGCTGCT	120
GTAAGCCTAT GCGGGGGTCT CCGCGGAGCC TTTGGCTACC AAGGTGCGGA GTATGTCATT	180
AGCCCTCTGC CCAACACCAG CGGCCTGAG GCGCAGCGTC ATAGCCAGGG CGCACACCTT	240
CTCCAGCGCC GGGGTGCTCC CGTAGGCCT TCCGGAGACC CTACCTCTCG CTGCGGGGTG	300
GCCTCGGGCT GGAACCCCGC CATCTGAGG GCCTTGGACC CTTATAAACC ACGGCGGACG	360
GGCGTGGGCG AAAGCCACAA CCGGCGCAGG TCTGGGCGCG CCAAGCGCTT CGTGTCTATA	420
CCACGGTACG TGGAGACACT GGTGGTGGCG GACGAGTCAA TGGTCAAGTT TCACGGCGCG	480
GATTTGGAAC ATTATCTGCT GACGCTGCTG GCCACGGCGG CGCGACTCTA CCGCCACCCC	540
AGCATCCTCA ACCCTATCAA CATCGTTGTG GTCAAGGTGT TACTCTTAGG AGATCGTGAC	600
ACTGGGCCCA AGGTCACAGG CAACGCGGCC CTGACTCTGC GCAACTTCTG TGCCTGGCAG	660
AAAAAGTTGA ACAAAGTGAG CGACAAGCAC CCCGAGTACT GGGACACAGC CATCCTCTTC	720
ACCAGACAGG ACCTATGCGG GGCTACCACC TGTGACACCT TGGGCATGGC TGATGTGGGC	780
ACCATGTGTG ATCCCAAGAG AAGCTGCTCT GTCATCGAGG ACGATGGGCT TCCGTCGGCC	840
TTCACCACTG CCCATGAGCT GGGCCATGTG TTCAACATGC CCCATGACAA CGTGAAGGTG	900
TGTGAGGAGG TGTTTGGGAA GCTCAGAGCC AACCACATGA TGTCTCCGAC ACTCATCCAG	960
ATCGACCGTG CCAACCCCTG GTCAGCCTGC AGTGCTGCCA TTATCACCGA CTTCTGGAC	1020
AGCGGGCAGG GTGACTGCCT CCTGGACCAG CCCAGCAAGC CCATCACCCCT GCCTGAGGAC	1080
CTGCCAGGCA CAAGCTACAG TTTGAGCCAA CAGTGCGAGC TGGCCTTTGG GGTGGGCTCT	1140
AAGCCCTGCC CATATATGCA GTACTGTACA AAGCTGTGGT GCACCGGCAA GGCCAAGGGG	1200
CAGATGGTGT GCCAGACTCG CCACTTCCCC TGGGCAGATG GCACCAGCTG TGGTGAGGGC	1260
AAGTTCTGCC TCAAGGGAGC CTGCGTGGAG AGACACAACC CAAACAAGTA CCGGGTGGAC	1320
GGCCCTTGGG CCAAGTGGGA GCCTTATGGT CCCTGCTCGC GCACCTGCGG TGGGGGCGCG	1380
CAGCTGGCCC GGAGGCAAGT GCAAGCAACC CTACCCCTGC CAACGGGCGG GAAGTACTGC	1440
GAGGGAGTGA GAGTGAAATA CCGATCTTGC AACTTGGAGC CCTGCCCCAG CTCAGCCTCT	1500
GGCAAGAGCT TCCGGGAA	1518

Fig. 13

16/39

THYRARAARAGQRLTGSSLDLRRCFYSGYVNAEPDSFAAVSLCGGLRGAFGYQGAEEYVISPLPNTSAPEAQRHSQGAHL
 LQRRGAPVGPSPGDPSTSRGVSAGWNPAILRALDPYKPRRTGVGESHNRSSGRKRFVSI PRYVETLVVADESMVKFHGA
 DLEHYLLTLATAARLYRHPSILNPIINIVVKVLLGDRDTGPKVTGNAALTLRNFCANQKKLNKVSOKHPEYWDAILF
 TRQDLGATTCDTLGMADVGTMCDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKVEEVFGKLRANHMMSPTLIQ
 IDRANPWSACSAIIITDFLDSGHGDCLLDQPSKPIITLPEDLPGTSYSLSQQCELAFGVGSKPCPYMQYCTKLWCTGKAKG
 QMVCQTRHFPWADGTSCGEGKFLKGACVERHNPKNYRVDPWAKWEYPGPCSRTCGGGAQLARRQVQATLPLPTGGKYC
 EGVVRVKYRSCNLEPCSSASGKSFR

Fig. 14

GATGCATCTAAGCCCTGGTCCAAATGCACCTCAGCCACCATCACAGAATTCCTGGATGATGGCCATGGTAACTGTTTGCT
 GGACCTACCACGAAAGCAGATCCTGGGCCCCGAAGAACTCCAGGACAGACCTACGATGCCACCCAGCAGTGCAACCTTA
 CATTCCGGCCTGAGTACTCCGTGTGTCCCGGCATGGATGTCTGTGCTCCCCTGTGGTGTGCTGTGGTACGCCAGGGCCAG
 ATGGTCTGTCTGACCAAGAAGCTTCCTGCGGTGGAAGGGACGCCTTGTTGAAAGGGGAGAATCTGCCTGCAGGGCAAATG
 TGTGGACAAAACCAAGAAAAAATATTATTCAACGTCAAGCCATGGCAACTGGGGATCTTGGGGATCCTGGGGCCAGTGTT
 CTCGCTCATGTGGAGGAGGAGTGCAGTTTGCCTATCGTCGCTGTAATAACCCTGCTCCCAGAAACAACGGACGCTACTGC
 ACAGGGAAGAGGGCCATCTACCGCTCCTGCAGTCTCATGCCCTGCCACCCCAATGGTAAATCATTTTCGTATGAACAGTG
 TGAGGCCAAAAATGGCTATCAGTCTGATGCAAAAGGAGTCAAAACTTTTGTGGAATGGGTTCCCAAAATATGCAAGTGTC
 TGCCCAGCGATGTGTGCAAGCTGACCTGCAGAGCCAAAGGGACTGGCTACTATGTGGTATTTTCTCCAAAGGTGACCGAT
 GGCACCTGAATGTAGGCCGTACAGTAATCCGTCTGCGTCCGGGGGAAGTGTGTGAGAACTGGCTGTGACGGCATCATTGG
 CTCAAAGCTGCAGTATGACAAGTGCAGGATATGTGGAGGAGACAACCTCAGCTGTACAAAGATTGTTGGAACCTTTAATA
 AGAAAAGTAAGGGTTCANCTGACGTGGTGAGGATTCCTGAAGGGGCAACCCACATAAAAGTTCGACAGTTCAAAGCCAAA
 GACCAGACTAGATTCAGTGCCTATTTAGCCCTGAAAAAGAAAAACGGTGAGTACCTTATCAATGGAAAGTACATGATCTC
 CACTTCAGAGACTATCATTGACATCAATGGAACAGTCATGAACTATAGCGGTTGGAGCCACAGGGATGACTTCCTGCATG
 GCATGGGCTACTCTGCCACGAAGGAAATCTAATAGTGCAGATTCTTGCAACAGACCCCACTAAACCATTAGATGTCCGT
 TATAGCTTTTTTTGTTCCCAAGAAGTCCACTCCAAAAGTAACTCTGTCACTAGTCATGGCAGCAATAAAGTGGGATCACA
 CACTTCGACGCCGAGTGGGTACGGGCCCATGGCTCGCTGCTCTAGGACCTGTGACACAGGTTGGCACACCAGAACGG
 TGCAGTGCCAGGATGGAAACCGGAAGTAGCAAAAGGATGTCTCTCTCCAAAGGCTTCTGCGTTTAAGCAATGCTTG
 TTGAAGAAATGTTAG

Fig. 15

17/39

DASKPWSKCTSATITEFLDDGHGNCLLDLPRKQILGPEELPGQTYDATQQCNLTFGPEYSVCPGMDVCAPLWCAVVRQQQ
MVCLTKKLPAVEGTPCGKGRICLOGKCVDTKKKYYSTSSHGNWGSWGSWGQCSRSCGGGVQFAYRRCNNPAPRNNGRYC
TGKRAIYRSCSLMPCPPNGKSFHEQCEAKNGYQSDAKGVKTFVEWVPKYASVLPDVCKLTCRAKGTGGYVVFSPKVTD
GTECRPYSNSVCVRGKCVRTGCDGIIGSKLQYDKCGVCGGDNSSCTKIVGTFNKKSXGSDVVRIPGATHIKVRQFKAK
DQTRFTAYLALKKKNGEYLINGKYMISTSETIIDINGTMNYSWGSRRDDFLHGMGYSATKEILIVQILATDPTKPLDVR
YSFFVPKKSTPKVNSVTSHGSNKVGSHTSQPQWVTGPWLACSRCTGTGWHTRTVQCQDGNRKLAKGCPLSQRPSAFKQCL
LKKC

Fig. 16

18/39

M - - - - -		Majority			
		10	20	30	40
1	M - - - - - G D V Q - R A A R S - - - - - R G S L S A H M L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
1	- - G I R - - - - -	hADAMTS-3			
1	L L G A R Q Y R R N S G P P T P A P E T S I A N S K H P A R L S R A A P P G A Q	rADAMTS-4			
1	M - - - - - S Q T G S H P G R G L A G R - - - - - W L W G A Q P C L L L	KIAA0688			
1	S L - - - - -	KIAA0366			
1	M D G R W Q C S - - - - -	KIAA0605			
- - - - - L L L L A L - T V L L S A D - - A G - P - - - E E E L		Majority			
		50	60	70	80
20	- - - - - L L L L A S I T M L L C A R G A H G R P T E E D E E L	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
41	R T M R L E W A S L L L L L L L C A S C L A L A A D N P A A A P A Q D K T R Q	rADAMTS-4			
27	P I V P L S W - - - L V W L L L L L L A S L L P S A R - - L A S P L P R E E E I	KIAA0688			
3	- - - - - W L I A A A L V E V R T S A D G Q A G N E E M V Q I D L	KIAA0366			
9	- - - - - C W A W F L L V L A V V A G D T V S T G S T O N S P T S N S L E G G T	KIAA0605			
V - - - - P - - - - L R G - - - P - G - - G T T S R L -		Majority			
		90	100	110	120
47	V L - - - P S - - - - - L E R A - - - P - G H D S T T T R L -	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - -	hADAMTS-3			
81	P R - - - A A A A A Q P D Q R Q W E E T Q E R G H L Q P L A R Q R R S S G L V	rADAMTS-4			
62	V F - - - P E - - - - - K L N G S V L P - G - S G T P A R L L	KIAA0688			
31	P I K R Y R E Y E L V T P V S T N L E G R Y L S H T L S A S H K K R S A R D V S	KIAA0366			
44	D A T A F W - - - - - W G E W T K W T A F S R S C G G G V T S Q E R	KIAA0605			
- N L D - - - - - G - - - - L - L E R D S G V - A P G - -		Majority			
		130	140	150	160
65	- R L D A F - - - - - G Q Q L H L K L Q P D S G F L A P G F T	mADAMTS-1			
1	- - - - -	hADAMTS-2			
4	- - - - - G R V D - - - - -	hADAMTS-3			
118	Q N I D Q L Y S G G G K V G Y L V Y A G G R R F L L D L E R D D T V G A A G G I	rADAMTS-4			
83	C R L Q A F - - - - - G E T L L L E L E Q D S G V Q V E G L T	KIAA0688			
71	S N P E Q L F - - - - - F N I T A F G K D F H L R L K P N T Q L V A P G A V	KIAA0366			
73	H C L Q - - - - - Q R R K S V P G P G - -	KIAA0605			

Fig. 17A

19/39

[illegible]

Fig. 17B

20/39

		-----GLAHT--S-----RRTKRFASEARF-	Majority
		330 340 350 360	
214	---	PVRDPTPOCAGKPSGPGS-----IRKKRFVSSPRY-	mADAMTS-1
1	---	-----RTKRFBVSEARF-	hADAMTS-2
108	ALNSGLATEAFSAYGNKTONTREKRTHRRTKRFLSYPRF-		hADAMTS-3
279	-----LLDHSASFSPAGNAGPQTW-----WRRRRRSISRARQ-		rADAMTS-4
209	-----RAKRFAFLSRF-		KIAA0688
232	NIHQQLNET-----MRRRRRHAGENDYN		KIAA0366
219	WYRKGNAGHLGYSLVTHIPAGARDIQIVERKK-----S		KIAA0605
		VEVLLVADDSMAAFHGAG-LQNYLLTLMSIAARIYKHPSI	Majority
		370 380 390 400	
244	VETMLVADQSMADFHGSG-LKHVELLTLFSVAARFYKHPSI		mADAMTS-1
12	VETLLVADASMAAFYGADELQNFELTLMSVAARIYKHPSI		hADAMTS-2
147	VEVLVADNRMVSYHGEN-LQHYELTLMSID-----		hADAMTS-3
310	VELLLVADSSMAKMYGRG-LQHYELTLASIANRLYSHASI		rADAMTS-4
220	VETLVVADDKMAAFHGAG-LKRYELTVMAAAAKAFKHPSI		KIAA0688
254	IEVLLGVDDSVVRFHGKEHVQNYLLTLMNIVNEIYHDESL		KIAA0366
251	ADVLALADEAGYYFFNG-----NYKVD-----SPKNFNIAGT		KIAA0605
		RNSISLVVVKVVLGDEKKGPEVSX-NAALTTLRNFCNWQH	Majority
		410 420 430 440	
283	RNSISLVVVKILVIYEEQKGPEVTS-NAALTTLRNFCNWQK		mADAMTS-1
51	KNSINLMVVKVLIVEDEKKGPEVSD-NGGLTLRNFCNWQR		hADAMTS-2
177	-----GPSISF-NAQTTLKNLQCWQH		hADAMTS-3
349	ENHIRLAVVKVVLTD--KSLEYSK-NAATTLKNFCWQH		rADAMTS-4
259	RNPVSLVVTRLVILGSGEEGPQVGP-SAAQTLRSFCWQR		KIAA0688
294	GVHINVVLVRMIMLGYSISLIERGNPSRSLENVCRWAS		KIAA0366
283	VVKYR-----RPHDVYETGIEYIVAQGPTNQGLNVM-VWNQ		KIAA0605
		QHNSPSDRHPEHYDTAILLTRQDLGSHG-CDTLGMADV G	Majority
		450 460 470 480	
322	QHNSPSDRDPPEHYDTAILLTRQDLGSHG-CDTLGMADV G		mADAMTS-1
90	RFNQPSDRHPEHYDTAILLTRQNFCCGQEGLCDTLGVADIG		hADAMTS-2
197	SKNSPGGI---HHD TAVLLTRQDICRAHDKCDTLGLAELG		hADAMTS-3
386	QHNLGDDHEEHYDAA!LFTREDLCGHHS-CDTLGMADV G		rADAMTS-4
298	GLNTPEDSDPDHFDTAILLTRQDLGCVST-CDTLGMADV G		KIAA0688
334	QQQRSDLNHSEHHDAIFLTRQDF-GPAGM---QGYAPVT		KIAA0366
318	NGKSPSIT---FEYTL LQPPHE---SRPQPIYYGFSESA		KIAA0605

Fig. 17C

SUBSTITUTE SHEET (RULE 26)

21/39

TICDPXRSCSVIEDDGLQAAFTVAHELGHVNLNMPHD-DSK																	Majority
<div>490500510520</div>																	
361	TVCCPSRSCSVIEDDGLQAAFTTAHELGHVFNMPHD-DAK																mADAMTS-1
130	TICDPNKSCSVIEDEGLQAAHTLAHELGHVLSMPHD-DSK																hADAMTS-2
234	TICDPYRSCSISEDGLSTAFTIAHELGHVFNMPHD-DNN																hADAMTS-3
425	TICSPERSCAVIEDDGLHAAFTVAHEIGHLLGLSHD-DSK																rADAMTS-4
337	TVCDPARSCAIVEDDGLQSAFTAHAHELGHVFNMLHD-NSK																KIAA0688
370	GMCHPVRSC TLNHEDGFSSAFVVAHETGHV LGMEHDGQGN																KIAA0366
351	-----ESQGLDGA-----GLMGFI PHNG---																KIAA0605
PC-SLNGPXGSSRHVM-APLLXHL DHSXPWSPCSAQEITE																	Majority
<div>530540550560</div>																	
400	HCA SLNGVTGDS-HLM-ASNLSSLDHSQPWSPCSAYMVT S																mADAMTS-1
169	POTRLFGPMGKH-HVM-APLFVHLNQTLPWSPCSAMYLT E																hADAMTS-2
273	KCKE---EGVKS PQHVM-APTLNFYTNPMWWSKCSRKYIT E																hADAMTS-3
464	FCEENFGS-TEDKRLM-SSILTSIDASKPWSKCTSATITE																rADAMTS-4
376	PCISLNGPLSTSRHVM-APVMAHVDPEEPWSPCSARFITD																KIAA0688
410	RC---GDETAMGSVM-APLVQAAFHRYHWSRCSGQELKR																KIAA0366
369	---SLYGQASSERLGLDNRLFGHPGLDMELGPSQGQETNE																KIAA0605
F-LONGHGDCLLDKPEA-PLPLPVELPG--ILYDADEQCQ																	Majority
<div>570580590600</div>																	
438	F-LONGHGECCLMDKPQN-PIKLPSDLPG--TLYDANRQCQ																mADAMTS-1
207	L-LGGGHGDCCLLDAPAA-ALPLPTGLPGRMALYQLDQCCR																hADAMTS-2
310	F-LDTGYGECCLNEPESRPYPPLPVQLPG--ILYNVNKQCE																hADAMTS-3
502	F-LDDGHGNCLLDVPRK-QILGPEELPGQT--YDATQCCN																rADAMTS-4
415	F-LONGYGHCLLDKPEA-PLHLPTVTFPGKD--YDADROCQ																KIAA0688
445	Y-IHSY--DCLLDDPFDHDPKLPPELPG--INYSMDEQCR																KIAA0366
406	VCEQAGGGAC-EGPPRGKGFRDRNVTGTPLTGDKDDEEVD																KIAA0605
LTFGPGSKHCPXFSA-DVCAQLWCAGVD-GGHXVCQTKHG																	Majority
<div>610620630640</div>																	
474	FTFGEEKSKHCPDAAS--TCTTLNCTGTS-GGLLVCQTKH-																mADAMTS-1
245	QIFGPDFRHCPNTSAQDVCAQLWCH-TD-GAEPLCHTKNG																hADAMTS-2
347	LIFGPGSQVCPYMMQ---CRRLWCNNVN-GVHKGCRTQHT																hADAMTS-3
538	LTFGPEYSVCPGM---DVCARLWAAVVR-QGQMVCLTKK-																rADAMTS-4
451	LTFGPDSRHCPQLPPP---CAALWCSGHL-NGHAMCQTKHS																KIAA0688
480	FDFGVGYKMCTAFRTFDPCQQLWCSPD-NPY-FCKTKKG																KIAA0366
445	THFASQ-----EFFSANAISDQLLGAGSDLKDFTLNETVNS																KIAA0605

Fig. 17D

SUBSTITUTE SHEET (RULE 26)

22/39

- - PWADGT P C G P G K W - C K A G S - C V P K E E N E R - - P V V D G G W		Majority
	650 660 670 680	
510	- F P W A D G T S C G E G K W - C V S G K - C V N K T D M K H F A T P V H G S W	mADAMTS-1
283	S L P W A D G T P C G P G H - C S E G S - C L P E E E V E R P K P V V D G G W	hADAMTS-2
383	- - P W A D G T E C E P G K H - C K Y G - F C V P K - E M C - - V P V T D G S W	hADAMTS-3
573	- L P A V R A L P V G K E E S A C K A N V W T K L R K N I T R H Q A M E I G G P	rADAMTS-4
488	- - P W A D G T P C G P A Q A - C M G G R - C L H M D Q L Q D F N I P Q A G G W	KIAA0688
518	- - P P L D G T E C A A G K W - C Y K G H - C M W K N A N Q Q - - - K Q D G N W	KIAA0366
481	I F A - - Q G A P - - - - - R S S L A E S F F V D Y E E N E - - - - -	KIAA0605
G P W G P W G D C S R T C G G S V Q F S L R E C N N P V P K N G G K Y C E G R -		Majority
	690 700 710 720	
547	G P W G P W G D C S R T C G G G V Q Y T M R E C D N P V P K N G G K Y C E G K -	mADAMTS-1
321	A P W G P W G E C S R T C G G G V Q F S H R E C K D P E P Q N G G R Y C L G R -	hADAMTS-2
416	G S W S P F G T C S R T C G G G I K T A ! R E C N R P E P K N G G K Y C V G R -	hADAMTS-3
612	G A P G V - - - - S V L A L A G E E Y S L P T A I A I T P H L E T V A A T A Q G	rADAMTS-4
524	G P W G P W G D C S R T C G G G V Q F S S R D C T R P V P R N G G K Y C E G R -	KIAA0688
551	G S W T K F G S C S R T C G T G V R F R T R Q C N N P M P ! N G G Q D C P G - V	KIAA0366
504	- - - - - G A G P Y L L H G S Y - - L E L S S D R V A N S S S	KIAA0605
R A K Y Q S C N T E D C P K H X G K T F R A E Q C A K Y N - A F S Y X N K G X X		Majority
	730 740 750 760	
586	R V R Y R S C N I E D C P D N N G K T F R E E Q C E A H N - E F S K A S F G N E	mADAMTS-1
360	R A K Y Q S C H T E E C P P D - G K S F R E Q Q C E K Y N - A Y N Y T D M D G N	hADAMTS-2
455	R M K F K S C N T E P C L K O K - R D F R D E Q C A H F D G K H F N I N - G L L	hADAMTS-3
648	R G P Y - T V P A V S Y P A H L T A N L S A T S S V K P K M A I S P M O K E S K	rADAMTS-4
563	R T R F R S C N T E D C P T G S A L T F R E E Q C A A Y N - H R T D L F K S F P	KIAA0688
590	N F E Y Q L C N T E E C Q K H F E - D F R A Q Q C Q Q R N S H F E Y Q N T K H -	KIAA0366
528	E A P F P N V S T S L L T S A G N R T H K A R T R P K A R K Q - - - - G V S P A	KIAA0605
P X V E W V P K Y A G V S P K D R C K L T C R A K G T G Y Y Y V L E P K V V D G		Majority
	770 780 790 800	
625	P T V E W T P K Y A G V S P K D R C K L T C E A K G I G Y F F V L Q P K V V D G	mADAMTS-1
398	- L L Q W V P K Y A G V S P R D R C K L F C R A R G R S E F K V F E A K V I D G	hADAMTS-2
493	P N V R W V P K Y S G I L M K D R C K L F C R V A G N T A Y Y Q L R D R V I D G	hADAMTS-3
687	T F V E W V P K Y A G V L P A D V C K L T C R A K G T G Y Y V V F S P K V T D G	rADAMTS-4
602	G P M D W V P R Y T G V A P O D Q C K L T C Q A R A L G Y Y V V L E P R V V D G	KIAA0688
628	- - - H W L P - Y E H P D P K K R C H L Y C Q S K E T G D V A Y M K Q L V H D G	KIAA0366
564	D M Y R W K - - - - - L S S H E P C S A T C T T G V M S A Y - - - - -	KIAA0605

Fig. 17E

23/39

TPCS - PDSNSVCVRGQCVKAGCDEIIGSKKKFQKCGVCGG		Majority
	810 820 830 840	
665	TPCS - PDSTSVQVQGGQCVKAGCDRIIDSKKKFQKCGVCGG	mADAMTS-1
437	TLCG - PETLAICVRGQCVKAGCDHVVDSEFWKLDKCGVCGG	hADAMTS-2
533	TPCG - QDTNDICVQGLCROAGCDHVLNSKARRDKCGVCGG	hADAMTS-3
727	TECR - PYSNSVCVRGRGCVRTGCDGIIGSKLQYDKCGVCGG	rADAMTS-4
642	TPCS - PDSSSVQVQGRCHAGCDRIIGSKKKFQKCMVCGG	KIAA0688
664	THCSYKDPYSICVRGECVKVVGCDKEIGSNKVEDKCGVCGG	KIAA0366
589	-----AMCVR-----	KIAA0605
DGSSCKKVSGTFTKT--RYGYNDVVTIPAGATN:LVQRQS		Majority
	850 860 870 880	
704	NGSTCKKMSGIVTST--RPGYHDIIVTIPAGATNIEVKHRN	mADAMTS-1
476	KGNSCRKSGSGLTP--VYGYNDIIVTIPAGATNIDVKQRS	hADAMTS-2
572	DNSSCKTVAGTFNTV--HYGYNTVVRIPAGATNIDVRQHS	hADAMTS-3
766	DNSSCTKIIIGTFNKK--SKGYTDVVRIPAGATHIKVRQFK	rADAMTS-4
681	DGSGCSKQSGSFRKF--RYGYNNVVTIPAGATHILVRQQG	KIAA0688
704	DNSHCRTVKGTFTTRTPRKLGYLKMFDIPPGARHVLIOEDE	KIAA0366
594	-----YDGV-----	KIAA0605
ASGHTN--NYLALKX-ADGEYLLNGNFTLSTSETDIDLKG		Majority
	890 900 910 920	
742	QRGSRNNGSFLAIRA-ADGTYILNGNFTLSTLEGDLTYKG	mADAMTS-1
514	HPGVQNDGNYLALKT-ADGQYLLNGNLAISAIEQDILVKG	hADAMTS-2
610	FSGETGDDNYLALSS-SKGFEYLLNGNFVVTMAKREIRIGN	hADAMTS-3
804	AKDQTRFTAYLALKK-KTGEYLLNGKYMISTSETIIDING	rADAMTS-4
719	NPGHRS--IYLALKL-PDGSYALNGEYTLMPSPDQVVLPG	KIAA0688
744	ASPH-----ILAIAKNQATGHYILNGKGEEAKSRTFIDL--	KIAA0366
598	-----	KIAA0605
TV-LRYSGSSAALERLHS-----PLKEPLTVQVLAV-GXT-		Majority
	930 940 950 960	
781	TV-LRYSGSSAALERIRS--FSPLKEPLTIQVLMV-GHAL	mADAMTS-1
553	TI-LKYSGSIATLERLQS--FRPLPEPLTVQLLAVPGEVF	hADAMTS-2
649	AV-VEYSGSETAVERINSTD--RIEQELLLQVLSV-GKLY	hADAMTS-3
843	TV-MNYSGWSHRDDFLHGMGYSATKEILIVQILA-TDPTK	rADAMTS-4
756	AVSLRYSGATAASETLSG--HGPLAOPLTQLVL-VAGNPQ	KIAA0688
777	GVEWDYN-IEDDIESLHTDG--PLHDPVIVLIIPQENDT-	KIAA0366
598	EVDDSYCDALTRPEPVHE-----	KIAA0605

Fig. 17F

24/39

R P D V R Y S F F V P - - - - -										Majority
970		980		990		1000				
817	R P K I K F T Y F M - - - - -									mADAMTS-1
590	P P K V K Y T F F V P N D - - - - -									hADAMTS-2
685	N P D V R Y S F N I P I E D K P - - - - -			Q Q F Y W N S H G P W Q						nADAMTS-3
881	A L D V R H S F F V P - - - - -									rADAMTS-4
793	D T R L R Y S F F V P - - - - -									KIAA0688
813	R S S L T Y K Y I I H E D S V P T I N S N N V I Q E E L D T F E W - A L K S W S									KIAA0366
616	- - - - - F C A G R E C Q P R - - - - -			W E T - S S W S						KIAA0605
- - - - -										Majority
1010		1020		1030		1040				
827	- - - - -									mADAMTS-1
603	- - - - -									hADAMTS-2
713	A C S K P C Q G E R K - R K L V C T R E S D - - - Q L T V S D Q R C D R L P Q P									hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - -									KIAA0688
852	Q V S K P C G G G F Q Y T K Y G C R R K S D - - - N K M V H R S F C E A N K K P									KIAA0366
633	E C S R T C G E G Y Q F R V V R C W K M L S P G F D S S V Y S D L C E A A E A V									KIAA0605
- - - - -										Majority
1050		1060		1070		1080				
827	- - - - -									mADAMTS-1
603	- - - - -			V - D F S - - -						hADAMTS-2
749	G H I - T E P C G T - D C D L R - W H V A S R S E C S A Q C G L - G Y R T L D I									hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - -									KIAA0688
889	K P I - R R M C N I Q E C T H P L W V A E E W E H C T K T C G S S G Y Q L R T V									KIAA0366
673	R P E E R K T C R N P A C G - P Q W E M S E W S E C T A K C G E R S V V T R D I									KIAA0605
- - - - - K V T - - - - S S N T R P T - R X X - - - - -										Majority
1090		1100		1110		1120				
827	- - - - - K K K T E - - - - S F N A I P T F - S E - - - - -									mADAMTS-1
607	- - - - - M Q S S K E R A T - - - - T N I T Q P L L H A Q - - - - -									hADAMTS-2
785	Y C A K Y S R L D G K T E K V D D G F C S S H P K P S N R E K C S G E C N T G G									hADAMTS-3
892	- - - - -									rADAMTS-4
804	- - - - - R P T - - - - P S T P R P T - P Q D - - - - -									KIAA0688
928	R C L Q - P L L D G T N R S V H S K Y C M G D - R P E S R R P C N R V P C P A Q									KIAA0366
712	R C S E - - - - - D E K L C D P N T R P V G E K N C T G P P C D R Q									KIAA0605

Fig. 17G

SUBSTITUTE SHEET (RULE 26)

25/39

WV - GDWGECSKTCG - GTQRRXV - CRD - DG - V - - - SEC - KA		Majority
	1130 1140 1150 1160	
842 WVIEEWGECSKTCGSGWQRRVVQCRDINGHP - - ASECAKE		mADAMTS-1
627 WVLGDWSECSSTCGAGWQRRRTVECRDP SGQA - - SATCNKA		hADAMTS-2
825 WRYSAWTECSKSCDGGTQRRRAICVNTRNDVLD DSKCTHQ		hADAMTS-3
892 - - - - -		rADAMTS-4
817 WL - - - - - H RRA - - - - - Q I		KIAA0688
966 WKTGPWSECSVTCEGEGTEVRQVLCRAGDHCDG EKPE SVRA		KIAA0366
741 WTVSDWGPSCSGSCGQGR TIRHVYCKTSDGRVVPESQCOM -		KIAA0605
- - LKPLXXRPC - - - KS - - CP - - W - - DWS - - - - - C - -		Majority
	1170 1180 1190 1200	
880 - - VKPASTRPC - - - ADLPCP - HWQVG DWSP - - - - - CSK		mADAMTS-1
665 - - LKPEDAKPC - - - ES - - - - -		hADAMTS-2
865 - - EKVTIQR - C - - - SEFP CP - QWKSG DWSE - - - - - CLV		hADAMTS-3
892 - - - - -		rADAMTS-4
825 - - LEILRRRP - - - - - WA - - - - -		KIAA0688
1006 CQLPPCNDEPCLGDKSIFCQ - MEVLARYCSIPGYNKL CCE		KIAA0366
780 - ETKPLAIHPC - GDKN - - CPAHWLAQDWER - - - - - CNT		KIAA0605
TCGK - - - - - KKPT -		Majority
	1210 1220 1230 1240	
907 TCGK - - - - - GYKKRTL		mADAMTS-1
676 - - - - -		hADAMTS-2
891 TCGK - - - - - GHKHRQV		hADAMTS-3
892 - - - - - KKPA X		rADAMTS-4
835 - - GR - - - - -		KIAA0688
1045 SCSKRSSTLPPPYLLEAAETHDDVISNP SDLP RSLVMPTS		KIAA0366
809 TCGRGVKKRLVLCMELANGKPQTRSGPECGLAK - - KPPEE		KIAA0605
KV - - - - - SA - - - - - DT		Majority
	1250 1260 1270 1280	
918 KCV - - - - - SH - - - - - DG		mADAMTS-1
676 - - - - -		hADAMTS-2
902 WCQFGEDRLNDRMCDPEVDAAANSA - - - - - DT		hADAMTS-3
897 KVN - - - - - SA - - - - - DT		rADAMTS-4
837 - - - - -		KIAA0688
1085 LVPYHSETPAKKMSLSSISSVGGPNAYAAFRPNSK - - PDG		KIAA0366
847 STCF - - ERPCFKWYTSPWSECTKTCGVGV MRDVKCYQGT		KIAA0605

Fig. 17H

SUBSTITUTE SHEET (RULE 26)

26/39

	D G L - Q E S P - - P - - - - - P - - K P - - - - Q L C P L S Q C	Majority
	1290 1300 1310 1320	
925	G V L S N E S C - - D - - - - - P L K K P K H Y I D F C T L T Q C	mADAMTS-1
676	- - - - - Q L C P L	hADAMTS-2
929	D G L Q E S S P - - P - - - - - I P I W K P S I F S H V - P S S R I	hADAMTS-3
904	D G L - Q E S S - - P - - - - - P	rADAMTS-4
837	- - - - -	KIAA0688
1123	A N L R Q R S A - - Q Q A G S K T V R L V T V P S S P P T K R V H L S S A S Q M	KIAA0366
885	D I V R G C D P L V K P V G R Q A C D L Q P C P T E P P D D S C Q D Q P G T N C	KIAA0605
	A - - - - -	Majority
	1330 1340 1350 1360	
951	S	mADAMTS-1
681		hADAMTS-2
955	P	hADAMTS-3
912		rADAMTS-4
837	K	KIAA0688
1161	A A A S F F A A S D S I G A S S Q A R T S K K D G K I I D N R R P T R S S T L E	KIAA0366
925	A L A I - - - - - K V N L C G H W Y Y S K A C C R - - - S C R P P H S	KIAA0605
	-	Majority
951	-	mADAMTS-1
681		hADAMTS-2
955		hADAMTS-3
912		rADAMTS-4
837		KIAA0688
1201	R	KIAA0366
951		KIAA0605

Fig. 17I

27/39

Bovine ADAMTS 4 DNA

TTTAGGGAGG AGCAGTGTGA GGCCAAAAAT GGATATCAGT CTGATGCAAA AGGAGTCAAA	60
ACGTTTGTGG AATGGGTTCC CAAATATGCT GGTGTCCTGC CCGGAGACGT GTGCAAACTG	120
ACCTGCAGAG CTAAGGGCAC TGGCTACTAC GTGGTGTTCCT CTCCAAAGGT GACCGATGGG	180
ACAGAGTGCA GGCCATACAG CAATTCCGTG TGTGTCCGGG GGAAGTGTGT GCGGACAGGC	240
TGTGACAGCA TCATTGGCTC GAAGCTGCAG TATGACAAAT GTGGCGTCTG TGGAGGAGAC	300
AACTCCAGTT GCACAAAGGT GGTCCGAACC TTCAATAAAA AAAGTAAGGG TTACACTGAC	360
GTCGTGAGGA TCCCGAAGG GGCCTCAC ATAAAAGTCC GACAGTTCAA AGCCAAAGAC	420
CAG	423

Fig. 18

Bovine ADAMTS 4 Protein

FREEQCEAKNGYQSDAKGVKTFVWPKYAGVLPQDVCKLTCRAKGTGYVVFSPKVTDGTECRPYSNSVCVRGKCVRTG
CDSIIIGSKLQYDKCGVCGGDNSSCTKVVGTFNKKSKGYTDVVRIPGATHIKVRQFKAKDQ

Fig. 19

28/39

Bovine 0688 DNA

GGAAACCCTG GCCATTGGA GCAACTACCT GGCCTGAAG CTCCCGATG GTCCTATGC	60
CCTCAACGGT GAATACACGC TGATCCCGTC CCCCACAGAC GTGGTACTGC CCGGGGCCGT	120
CAGCCTGCCG TACAGCGGGG CCACTGCAGC CTGGGAGACA CTGTCAGGAC ACGGGCCCCT	180
GGCTGAGCCC TTAACGCTGC AGGTCCTAGT GGCTGGCAAC CCGCAGAAG CCCGCCTCAG	240
ATACAGCTTT TTCGTGCCG GACCGCGACC GGTCCCCTCC ACGCCACGCC CCACTCCCCA	300
GGACTGGCTG CGCCGCAAGT CACAGATTCT GGAGATCCTC CGGCGGCGCT CCTGGGCCGG	360
CAGGAAATAA CCTCACCATC CCGGCTGCCC TTTCTGGGCA CCGGGGCCTC GGACTTAGCT	420
GGGTGAACGA GAGACCTCTG CAGCGGCCTC ACCCCGAGAC ATCGTGGGG AGGGGCTTAG	480
TGAGCCCCGC CTCTCCTCCC CGCGTACCG AGCAGGCTGG CCCTGCCGGG GTTTCCTGCC	540
CTGGATGGCT GGTGGATGGA AGGGGCTGG AGATTGTCCC CTATCTAAAC TGCCCCCTCT	600
GCCCTGCTGG TCACAGGAGG GAGGGGGAAG GCAGGGA	637

Fig. 20

Bovine KIAA 0688 Protein

ETLAIWSNYLALKLPDGSYALNGEYTLIPSPDQVVLPGAVSLRYSGATAAETLSGHGPLAEPLTLQVLVAGNPQARLR
YSFFVPRPRVPSTPRPTQDWLRRKSQILEILRRRSWAGRK

Fig. 21

29/39

Human ADAMTS 5 DNA

```

ACTCACTATA GGGCTCGTGC GGCCGCCCGG GCAGGTATCT TTAAGCATCC CAGCATCCTC   60
AACCCCATCA ACATCGTTGT GGTCAAGGTG CTGCTTCTTA GAGATCGTGA CTCCGGGCCC   120
AAGGTCACCG GCAATGCGGC CCTGACGCTG CGCAACTTCT GTGCCTGGCA GAAGAAGCTG   180
AACAAAGTGA GTGACAAGCA CCCCAGTAC TGGGACACTG CCATCCTCTT CACCAGGCAG   240
GACCTGTGTG GAGCCACCAC CTGTGACACC CTGGGCATGG CTGATGTGGG TACCATGTGT   300
GACCCCAAGA GAAGCTGCTC TGTCATTGAG GACGATGGGC TTCCATCAGC CTTCAACCACT   360
GCCCACGAGC TGGGCCACGT GTTCAACATG CCCCATGACA ATGTGAAAGT CTGTGAGGAG   420
GTGTTTGGGA AGCTCCGAGC CAACCACATG ATGTCCCGA CCCTCATCCA GATCGACCGT   480
GCCAACCCTT GGTGAGCCTG CAGTGCTGCC ATCATACCG ACTTTCTGGA CAGCGGGCAC   540
GGTGACTGCC TCCTGGACCA ACCCAGCAAG CCCATCTTCC TGCCGAGNGA TCTGCCGGGC   600
GCCAGCTACA CCTGAGCCA GCARTGCGAG CTGGCTTTTG GCGTGGGCTT CAAGCCCTGT   660
CCTTACATGC AGTACTGCAC CAAGCTGTGG TGCACCGGGA AGGCCAAGGG ACAGATGGTG   720
TGCCAAACCC GCCACTTCCC CTGGGCCGAT GGCACCAGTT GTGGCGAGGG CAAGTTCTGC   780
CTCAAAGGGG CCTGCGTGA AARACACAAC CTCAACAAGC ACAGGGTGA TGTTCTCTGG   840
GCCAATGGG ATCCCTATGG CCCCTGCTCG CGCACATGTG GTGGGGCGT GCAGCTGGCC   900
AGGAGGCAGN TGCACCAACC CCANCCCTG CCAACNGGG GCAAGTACTG CGAGGGAGTG   960
AGGGTGAAAT ACCGATCCTG CAACCTGGAG CCCTGCCCA GCTCAGCCTC CGGAAAGAGC  1020
TTCCGGGAGG AGCAGTGTGA GGCTTTCAAC GGCTACAACC ACAGACCAA CCGGCTCACT  1080
CTCGCGTGG CATGGGTGCC CAAGTACTCC GCGTGTCTC CCCGTGACAA GTGTAAGCTC  1140
ATC                                     1143

```

Fig. 22

Human ADAMTS 5 Protein

```

THYRARAARAGIFKHPSILNPIINIVVKVLLLRDRDSGPKVTGNAALTLRNFCAWQKLNKVSOKHPEYWDTAILFTRQ
DLCGATTCDTLGMADVGTMDPKRSCSVIEDDGLPSAFTTAHELGHVFNMPHDNVKCEEVFGKLRANHMMSPTLIQIDR
ANPWSACSAAIITDFLSGHGDCLLDQPSKPIFLPXDLPGASYTLSQCELAFGVGFKPCPYMQYCTKLWCTGKAKGMV
CQTRHFPWADGTSCGEGKFLKGACVEXHNLNKHVRDGSWAKWDPYGPCSRTCGGGVQLARRQXHQPXPLPTGGKYCEGV
RVKYRSCNLEPCSSASGKSFREEQCEAFNGYNHSTNRLTLAVAWVPKYSYSPRKCKLI

```

Fig. 23

30/39

Rat ADAMTS 2 DNA

TCCGCCCTTC	CGGGAGGAAC	AGTGTGAAAA	ATATAATGCC	TACAACCACA	CGGACCTGGA	60
TGGGAATTC	CTTCAGTGGG	TCCCCAAATA	CTCAGGAGTG	TCCCCCGAG	ACCGATGCAA	120
ACTGTTTTGC	AGAGCCCGTG	GGAGGAGTGA	GTTCAAAGTG	TTTGAAACTA	AGGTGATCGA	180
TGGCACTCTG	TGCGGACCGG	ATACTCTGGC	CATCTGTGTG	CGGGGACAGT	GCGTTAAGGC	240
TGGCTGTGAC	CATGTGGTGA	ACTCACCTAA	GAAGCTGGAC	AAGTGCGGTA	TCTGTGG	297

Fig. 24

Rat ADAMTS 2 Protein

PPFREEQCEKYNAYNHTDLDGNFLQWVPKYSGVSPDRCKLFCRARGRSEFKVFETKVIDGTL CGPDTLAICVRGQCVKA
GCDHVVNSPKLDKCGIC

Fig. 25

31/39

Rat ADAMTS 3 DNA

```

CCCCTGGATG TGGTCAAAGT GCAGTCGGAA GTACATCACC GAGTTCTTAG AACTGGGTA      60
TGGAGAGTGC TTGTTAAATG AACCTCAATC CAGGACCTAT CCTTTGCCCT CCCAACTGCC      120
CGGCCTTCTC TACAACGTGA ATAAACAATG TGAAGTATT TTTGGACCAG GCTCTCAAGT      180
GTGCCCATAT ATGATGCAGT GCAGACGGCT CTGGTGCAAT AACGTGGATG GAGCACACAA      240
AGGCTGCAGG ACTCAGCACA CGCCCTGGGC AGATGGAACC GAGTGTGAGC CTGGAAAGCA      300
CTGCAAGTTT GGATTCTGTG TTCCCAAAGA AATGGAGGGC CCTGCAATTG ATGGATCCTG      360
GGGAAGTTGG AGTCACTTTG GGGCCTGCTC AAGAACATGT GGAGGAGGCA TCAGAACAGC      420
CATCAGAGAG TGCAACAGAC CAGAGCCAAA AAATGGTGGG AGGTACTGTG TAGGGAGGAG      480
AATRAAGTTC AAATCCTGCA ACACCGAGCC CTGCCCAGAG CACAAGCGAG ACTTCCGTGA      540
GGAGCAGTGT GCTTACTTTG ACGGCAAGCA TTTCAACATC AATGGTCTGC TGCCCAAGTGT      600
ACGCTGGGTC CCTAAGTACA GTGGAATTTT GATGAAGGAC CGATGCAAGT TGTCTGCAG      660
AGTGGCAGGA AACACAGCCT ACTACCAGCT TCGAGACAGA GTGATTGACG GAACCCCTG      720
TGGCCAGGAC ACAAATGACA TCTGTGTCCA AGGCCTTTGC CGGCAAGCTG GATGTGATCA      780
TACTTTAAAC TCAAAGGCCG GAAAGATAA ATGTGGGATT TGT                        823

```

Fig. 26

Rat ADAMTS 3 Protein

```

PMMWSKSRKYITEFLDTGYGECLLNEPQSRITYPLPSQLPGLLYNVNKQCELIFGPGSQVCPYMQCRRLWCNNVDGAHK
GCRTQHTPWADGTECEPGKHCKFGFCVPKEMEGPAIDGSWGSWSHFGACSRTCGGGIRTAIRECNRPEPKNGGRYCVGRR
XKFKSCNTEPCPKHKRDFREEQCA YFDGKHFNINGLLPSVRWVPKYSGLMKDRCKLFCRVAGNTAYYQLRDRVIDGTPC
GQDTNDICVQGLCRQAGCDHTLNSKARKDKCGIC

```

Fig. 27

32/39

brevican + TS-4

brevican

Fig. 28

SUBSTITUTE SHEET (RULE 26)

34/39

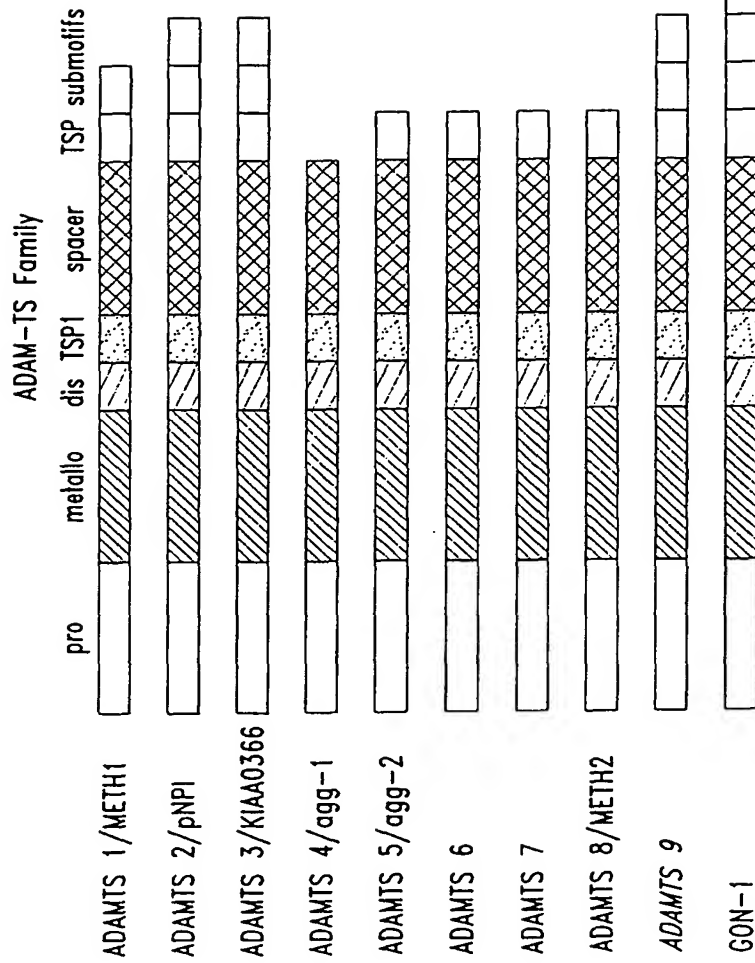


Fig. 30A

35/39

CONSENSUS	HEXXHXXGXXHD
Fertilin α	HELGHNLGIRHD
ADAM 17/TACE	HELGHNFGAEHD
ADAM 10/Kuz	HEIGHNFGSPHD
ADAMTS 1	HELGHVFNMPHD
ADAMTS 2	HETGHVLGMEHD
ADAMTS 4	HELGHVFNMLHD
ADAMTS 5	HEIGHLLGLSHD
ADAMTS 9	HELGHVFNMPHD
GON-1	HELGHVFSIPHD

Fig. 30B

36/39

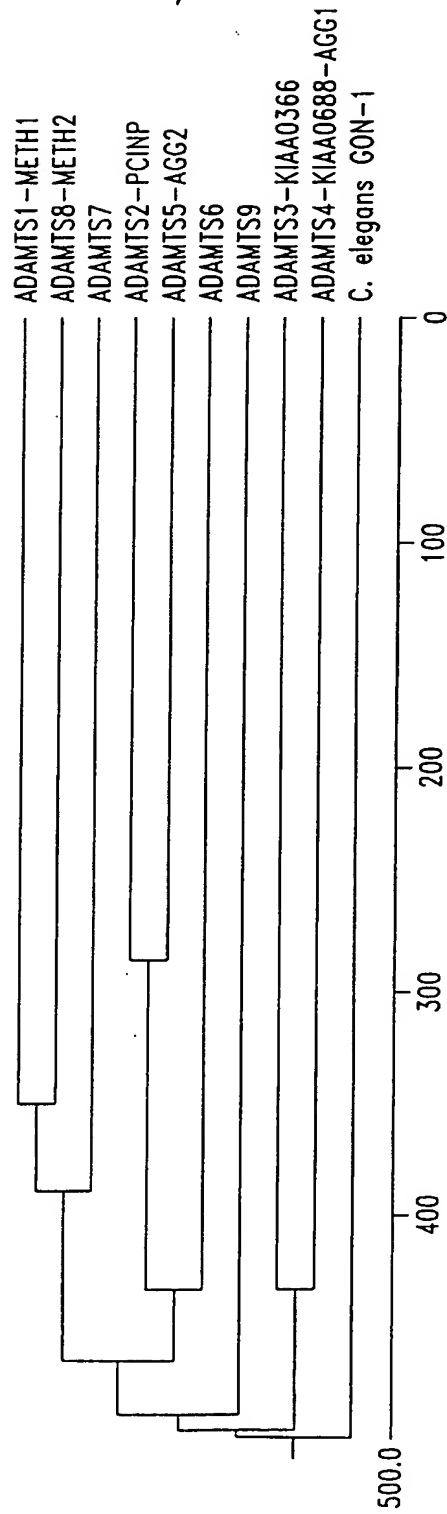


Fig. 30C

37/39

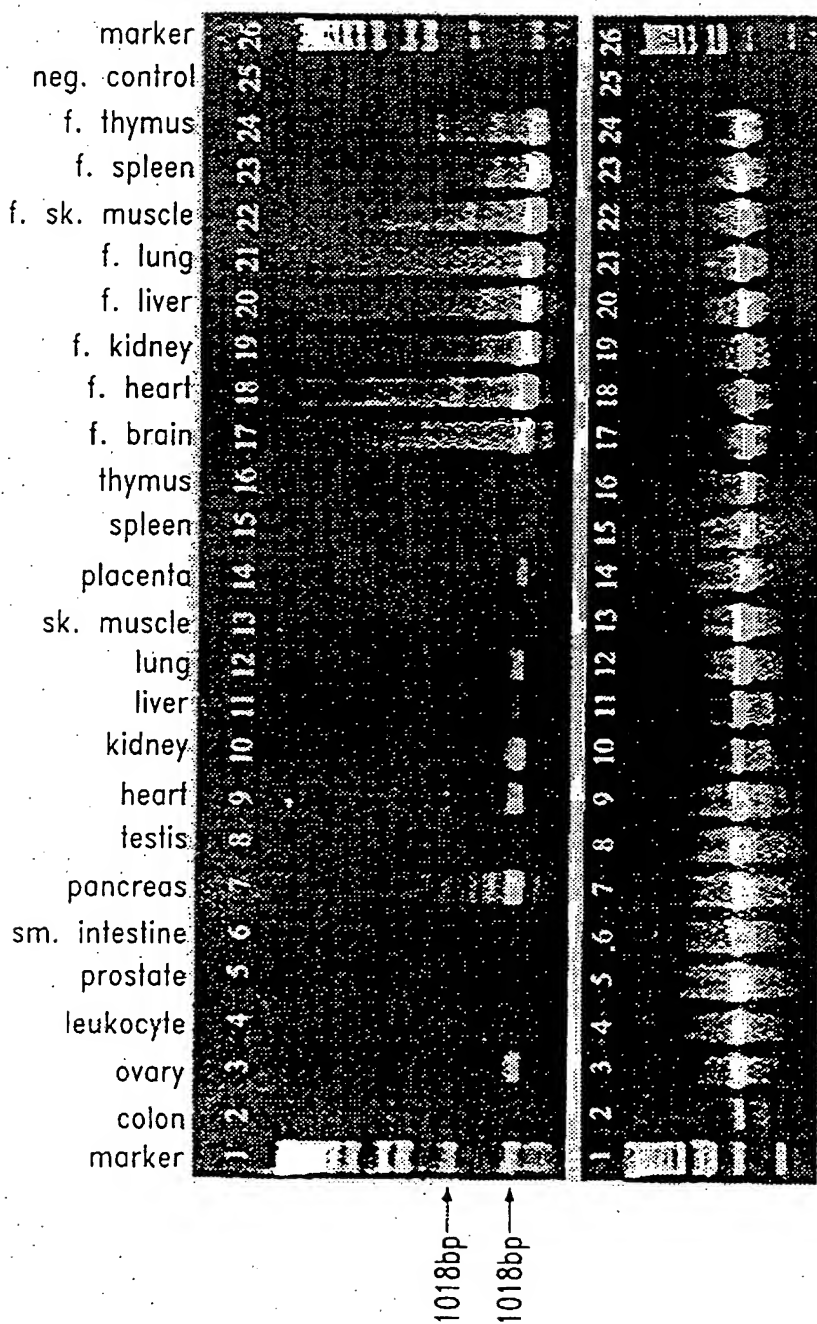


Fig. 31

38/39

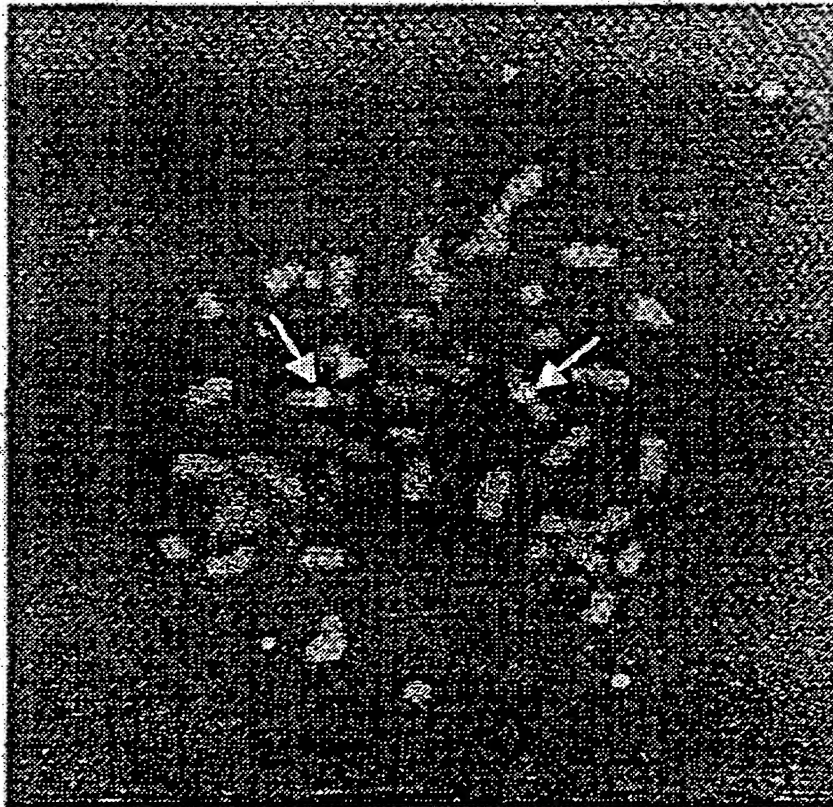


Fig. 32A

39/39

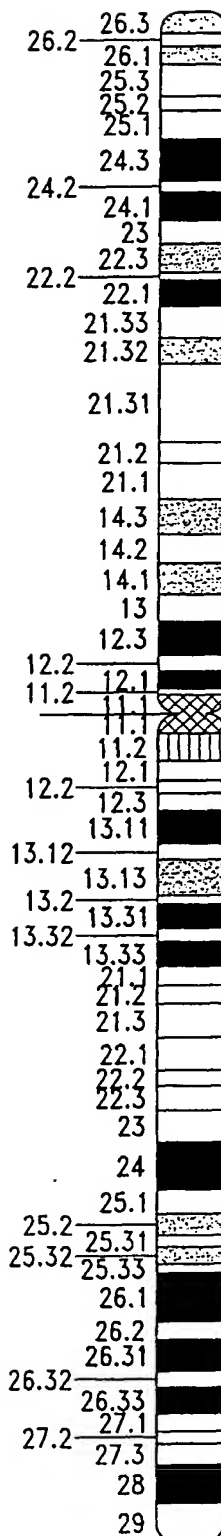
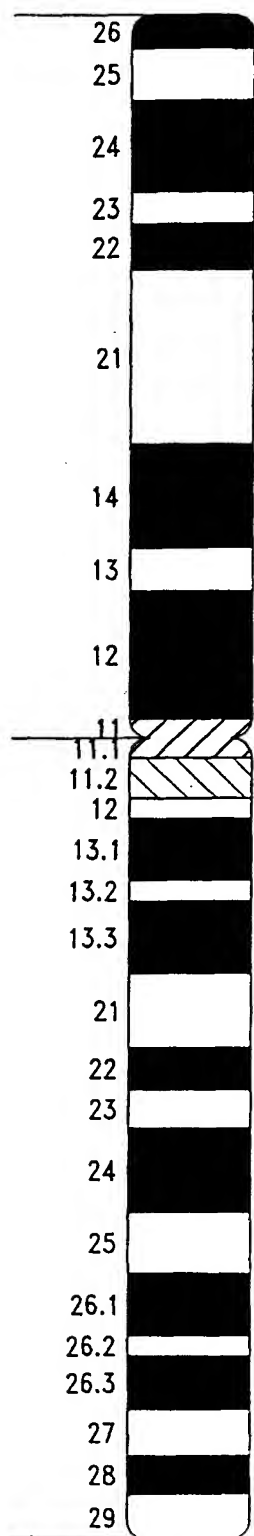


Fig. 32B

SEQUENCE LISTING

<110> Neurocrine Biosciences, Inc.
Kelner, Gregory S.
Clark, Melody
Maki, Richard A.

<120> METALLOPROTEINASES AND METHODS OF USE
THEREFOR

<130> 690068.453PC

<140> PCT

<141> 2000-03-08

<160> 51

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 2346

<212> DNA

<213> Homo sapien

<400> 1

aggaccaagc	ggtttgtgtc	tgaggcgcgc	ttcgtggaga	cgctgctggt	ggccgatgcg	60
tccatggctg	ccttctacgg	ggccgacctg	cagaaccaca	tcctgacgtt	aatgtctgtg	120
gcagcccgaa	tctacaagca	ccccagcatc	aagaattcca	tcaacctgat	ggtggtaaaa	180
gtgctgatcg	tagaagatga	aaaatggggc	ccagaggtgt	ccgacaatgg	ggggcttaca	240
ctgcgtaact	tctgcaactg	gcagcggcgt	ttcaaccagc	ccagcgaccg	gcacccagag	300
cactacgaca	cggccatcct	gctcaccaga	cagaacttct	gtgggcagga	ggggctgtgt	360
gacaccctgg	gtgtggcaga	catcgggacc	atttgtgacc	ccaacaaaag	ctgctccgtg	420
atcaggatga	aggggctcca	ggcggcccac	accctggccc	atgaactagg	gcacgtcctc	480
agcatgcccc	acgacgactc	caagccctgc	acacggctct	tcgggcccac	gggcaagcac	540
cacgtgatgg	caccgctggt	cgtccacctg	aaccagacgc	tgccctggtc	ccccctgcagc	600
gccatgtatc	tcacagagct	tctggacggc	gggcacggag	actgtctcct	ggatgcccct	660
gctgcggccc	tgccccctcc	cacaggcctc	ccgggcccga	tgccctgta	ccagctggac	720
cagcagtgca	ggcagatctt	tgggccggat	ttccgccact	gccccaacac	ctctgctcag	780
gacgtctgcg	cccagctttg	gtgccacact	gatggggctg	agcccctgtg	ccacacgaag	840
aatggcagcc	tgccctgggc	tgacggcacg	ccgtgcgggc	ctgggcacct	ctgctcagaa	900
ggcagctgtc	tacctgagga	ggaagtggag	aggcccaagc	ccgtggtaga	tggaggctgg	960
gcaccgtggg	gaccctgggg	agaatgttct	cggacctgtg	gaggaggagt	acagttttca	1020
caccgtgagt	gcaaggaccc	cgagcctcag	aatggaggaa	gatactgcct	gggtcggaga	1080
gccaagtacc	agtcatgcca	cacggaggaa	tgccccctg	acgggaaaag	cttcagggag	1140
cagcagtgtg	agaagtataa	tgctacaat	tacactgaca	tgacgggaa	tctcctgcag	1200
tgggtcccca	agtatgctgg	ggtgtccccc	cgggacgct	gcaagttgtt	ctgccgagcc	1260
cgggggagga	gcgagttcaa	agtgttcgag	gccaaaggtga	ttgatggcac	cctgtgtggg	1320
ccagaaacac	tggccatctg	tgtccgtggc	cagtgtgtca	aggccggctg	tgacctgtg	1380
gtggactcgt	tttggaagct	ggacaaatgc	ggggtgtgtg	gggggaaagg	caactcctgc	1440
aggaagggct	ccgggtccct	caccccacc	aattatggct	acaatgacat	tgtcaccatc	1500
ccagctgggtg	ccactaatat	tgacgtgaag	cagcggagcc	acccgggtgt	gcagaacgat	1560
gggaactacc	tggcgctgaa	gacggctgat	gggcagtacc	tgctcaacgg	caacctggcc	1620
atctctgcca	tagagcagga	catcttggtg	aaggggacca	tcctgaagta	cagcggctcc	1680

```

atcgccaccc tggagcgcct gcagagcttc cggcccttgc cagagcctct gacagtgcag 1740
ctcctggcag tccctggcga ggtcttcccc ccaaaagtca aatacacctt ctttgttcct 1800
aatgacgtgg acttttagcat gcagagcagc aaagagagag caaccaccaa catcacccag 1860
ccgctgctcc acgcacagtg ggtgctgggg gactggtctg agtgctctag cacctgcggg 1920
gccggctggc agaggcgaac tgtagagtgc agggacccct ccggccaggc ctctgccacc 1980
tgcaacaagg ctctgaaacc cgaggatgcc aagccctgcg aaagccagct gtgccccctg 2040
tgattcaggg gggcaggggc cagtcttggtg ctcctggaca tgcggtactg aggtgcagac 2100
aagggctctc actgtggtga ctgggtccct tggccatata aaggcagcac ggcccaccca 2160
ggcctcccat tgccgcaacc cctccagtac tgcacaaatt cctaaggggg aagaggagag 2220
ggtatggggc ggcagaccct atcatcaact gtccagtggg ctggaccttg ctcgggttca 2280
agtagagggc ataggttaaa aggtaaaagt gcacttattg taccagacag gacgcccgcg 2340
aattcg 2346

```

<210> 2

<211> 680

<212> PRT

<213> Homo sapien

<400> 2

```

Arg Thr Lys Arg Phe Val Ser Glu Ala Arg Phe Val Glu Thr Leu Leu
1          5          10          15
Val Ala Asp Ala Ser Met Ala Ala Phe Tyr Gly Ala Asp Leu Gln Asn
20          25          30
His Ile Leu Thr Leu Met Ser Val Ala Ala Arg Ile Tyr Lys His Pro
35          40          45
Ser Ile Lys Asn Ser Ile Asn Leu Met Val Val Lys Val Leu Ile Val
50          55          60
Glu Asp Glu Lys Trp Gly Pro Glu Val Ser Asp Asn Gly Gly Leu Thr
65          70          75          80
Leu Arg Asn Phe Cys Asn Trp Gln Arg Arg Phe Asn Gln Pro Ser Asp
85          90          95
Arg His Pro Glu His Tyr Asp Thr Ala Ile Leu Leu Thr Arg Gln Asn
100          105          110
Phe Cys Gly Gln Glu Gly Leu Cys Asp Thr Leu Gly Val Ala Asp Ile
115          120          125
Gly Thr Ile Cys Asp Pro Asn Lys Ser Cys Ser Val Ile Glu Asp Glu
130          135          140
Gly Leu Gln Ala Ala His Thr Leu Ala His Glu Leu Gly His Val Leu
145          150          155          160
Ser Met Pro His Asp Ser Lys Pro Cys Thr Arg Leu Phe Gly Pro
165          170          175
Met Gly Lys His His Val Met Ala Pro Leu Phe Val His Leu Asn Gln
180          185          190
Thr Leu Pro Trp Ser Pro Cys Ser Ala Met Tyr Leu Thr Glu Leu Leu
195          200          205
Asp Gly Gly His Gly Asp Cys Leu Leu Asp Ala Pro Ala Ala Ala Leu
210          215          220
Pro Leu Pro Thr Gly Leu Pro Gly Arg Met Ala Leu Tyr Gln Leu Asp
225          230          235          240
Gln Gln Cys Arg Gln Ile Phe Gly Pro Asp Phe Arg His Cys Pro Asn
245          250          255
Thr Ser Ala Gln Asp Val Cys Ala Gln Leu Trp Cys His Thr Asp Gly
260          265          270
Ala Glu Pro Leu Cys His Thr Lys Asn Gly Ser Leu Pro Trp Ala Asp
275          280          285

```

Gly Thr Pro Cys Gly Pro Gly His Leu Cys Ser Glu Gly Ser Cys Leu
 290 295 300
 Pro Glu Glu Glu Val Glu Arg Pro Lys Pro Val Val Asp Gly Gly Trp
 305 310 315 320
 Ala Pro Trp Gly Pro Trp Gly Glu Cys Ser Arg Thr Cys Gly Gly Gly
 325 330 335
 Val Gln Phe Ser His Arg Glu Cys Lys Asp Pro Glu Pro Gln Asn Gly
 340 345 350
 Gly Arg Tyr Cys Leu Gly Arg Arg Ala Lys Tyr Gln Ser Cys His Thr
 355 360 365
 Glu Glu Cys Pro Pro Asp Gly Lys Ser Phe Arg Glu Gln Gln Cys Glu
 370 375 380
 Lys Tyr Asn Ala Tyr Asn Tyr Thr Asp Met Asp Gly Asn Leu Leu Gln
 385 390 395 400
 Trp Val Pro Lys Tyr Ala Gly Val Ser Pro Arg Asp Arg Cys Lys Leu
 405 410 415
 Phe Cys Arg Ala Arg Gly Arg Ser Glu Phe Lys Val Phe Glu Ala Lys
 420 425 430
 Val Ile Asp Gly Thr Leu Cys Gly Pro Glu Thr Leu Ala Ile Cys Val
 435 440 445
 Arg Gly Gln Cys Val Lys Ala Gly Cys Asp His Val Val Asp Ser Phe
 450 455 460
 Trp Lys Leu Asp Lys Cys Gly Val Cys Gly Gly Lys Gly Asn Ser Cys
 465 470 475 480
 Arg Lys Gly Ser Gly Ser Leu Thr Pro Thr Asn Tyr Gly Tyr Asn Asp
 485 490 495
 Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Lys Gln Arg
 500 505 510
 Ser His Pro Gly Val Gln Asn Asp Gly Asn Tyr Leu Ala Leu Lys Thr
 515 520 525
 Ala Asp Gly Gln Tyr Leu Leu Asn Gly Asn Leu Ala Ile Ser Ala Ile
 530 535 540
 Glu Gln Asp Ile Leu Val Lys Gly Thr Ile Leu Lys Tyr Ser Gly Ser
 545 550 555 560
 Ile Ala Thr Leu Glu Arg Leu Gln Ser Phe Arg Pro Leu Pro Glu Pro
 565 570 575
 Leu Thr Val Gln Leu Leu Ala Val Pro Gly Glu Val Phe Pro Pro Lys
 580 585 590
 Val Lys Tyr Thr Phe Phe Val Pro Asn Asp Val Asp Phe Ser Met Gln
 595 600 605
 Ser Ser Lys Glu Arg Ala Thr Thr Asn Ile Thr Gln Pro Leu Leu His
 610 615 620
 Ala Gln Trp Val Leu Gly Asp Trp Ser Glu Cys Ser Ser Thr Cys Gly
 625 630 635 640
 Ala Gly Trp Gln Arg Arg Thr Val Glu Cys Arg Asp Pro Ser Gly Gln
 645 650 655
 Ala Ser Ala Thr Cys Asn Lys Ala Leu Lys Pro Glu Asp Ala Lys Pro
 660 665 670
 Cys Glu Ser Gln Leu Cys Pro Leu
 675 680

<210> 3

<211> 2751

<212> DNA

<213> Rattus norvegicus

<400> 3

```

ccccccctcg aggtcgacgg tatcgataag cttgatatcg aattccgggc cccccacccc 60
cgccccctgaa acttctatag caaatagcaa acatccagct agactcagtc gcgcagcccc 120
tcccggcggg cagcgacta tgccggctcga gtgggcgtcc ttgctgtgc tactgtgtg 180
gctgtgcgcg tectgcctgg ccctggccgc tgacaaccct gccgcggcac ctgcccagga 240
taaaaccagg cagcctcggg ctgctgcagc ggctgccag cccgaccagc ggcaagtggga 300
ggaaacacag gagcggggcc atctgcaacc cttggccagg cagcgagga gcagcgggct 360
gggtgcagaat atagaccaac tctactctgg cgggtggcaaa gtgggctacc ttgtctacgc 420
ggggcgccgg aggttcctgc tggacctgga gagggatgac acagtgggtg ctgctgggtg 480
catcgttact gcaggagggc tgagcgcac ctctggccac aggggtcact gcttctacag 540
aggcactgtg gacggcagcc ctcgatccct agctgtcttt gacctctgtg ggggtctcga 600
tggcttcttc gcagtcaagc atgcgcgcta cactctgagg ccgctcttgc gtgggtcctg 660
ggcagagtcc gaacgagtct acggggatgg gtcttcacgc atcctgcag tctacaccg 720
cgagggtctc agcttcgagg ccctgccgcc acgcaccagt tgcgagactc cagcgtcccc 780
gtctggggcc caagagagcc cctcggtgca cagtagttct aggcgacgca cagaactggc 840
accgcagctg ctggaccatt cagctttctc gccagctggg aacgcgggac ctgagacctg 900
gtggaggcgg aggcgcgctt ccatctccag ggcccggcag gtggagctcc tcttgggtgg 960
tgactcttcc atggccaaga tgtatgggcy gggcctgcag cattacctgc tgacctggc 1020
ctctattgcc aaccggctgt acagtcagc aagcatcgag aaccacatcc gcctggcgt 1080
agtgaagtgt gtggtgtga ccgacaagag tctggaggtg agcaagaacg cggccacgac 1140
cctcaagaac ttttgcaaat ggcagacca acacaaccag ctaggatgat accatgagga 1200
gcactacgat gcagccatcc tgttcaccag agaggattta tgtgggcac attcatgtga 1260
caccctggga atggcagacg ttgggaccat atgttctccg gagcgcagct gcgctgtgat 1320
tgaagtatg ggcctccatg cagctttcac tgtggctcac gaaattggac atctacttgg 1380
cctctctcac gcagattcca aattctgtga agagaacttt gggtctacag aagacaagcg 1440
tttaattgtc tcaatcctta ccagcattga tgcattcaag ccctgggtcca aatgcacttc 1500
agccacgac acagaatttc tggatgacgg tcatggtaac tgtttactag atgtaccacg 1560
gaagcagatt ctgggccccg aggaactccc aggacagacc tatgatgcca cccagcagtg 1620
caacttgaca tttgggctcg aatactctgt gtgccttggc atggatgtct gtgcacggct 1680
gtggtgtgct gtggtgccc aaggccaaat ggtgtgtctg accaagaagt tgctgtcgt 1740
ggagggcact ccctgtggga aaggaagaat ctgcctgcaa ggcaaatgtg tggacaaaac 1800
taagaaaaaa tattactcga catcaagcca tggaaattgg gggctctggg gccctgggg 1860
tcagtgttct cgctcttgcg ggggaggagt acagtttgcc taccgccatt gcaataaccc 1920
cgcacctcga aacagtggcc gctactgcac agggaaagagg gccatatacc gttcctgcag 1980
tgtcataccc tgcccaccta acggcaaatc tttccgccac gagcagtgtg aagccaaaaa 2040
tggctatcag tccgatgcaa aaggagtcaa aacatttcta gaatgggttc ccaaatacgc 2100
aggtgtcctg ccggcagacg tgtgcaagct tacgtgcaga gctaagggca ctggctatta 2160
cgtggtcttt tctccaaagg ttacagatgg gacagaatgt agaccctaca gcaactccgt 2220
gtgtgtccga gggaggtgcg tgagaacggg gtgtgacggc atcatcggtc caaagctaca 2280
gtatgacaag tgtggagtgt gtggagggga taactccagt tgtacaaaga ttatcggaac 2340
cttcaataaa aaaagcaagg gttatactga cgttgtgagg atccctgaag gagcaaccca 2400
cataaaagtc cgacagttca aagccmaaga ccagactaga ttactgctt acttagccct 2460
aaagaagaaa actggcgagt accttatcaa cggcaagtac atgatctcca cttcagagac 2520
catcatcgac atcaatggta ccgtcatgaa ctacagtggg tggagtcaaa gagatgattt 2580
tttacatggg atgggctatt cagccacaaa ggaaattctg attgtgcaga tccttgcaac 2640
agacccaact aaagcattag acgtccgtta cagctttttt gttcccaaga agaccactca 2700
aaaagtgaat tcctgcagcc cgggggatcc actagtctta gagcggccgg b 2751

```

<210> 4

<211> 870

<212> PRT

<213> Rattus norvegicus

<220>

<221> VARIANT

<222> (1)...(870)

<223> Xaa = Any Amino Acid

<400> 4

```

Met Arg Leu Glu Trp Ala Ser Leu Leu Leu Leu Leu Leu Leu Cys
 1           5           10           15
Ala Ser Cys Leu Ala Leu Ala Ala Asp Asn Pro Ala Ala Ala Pro Ala
 20           25           30
Gln Asp Lys Thr Arg Gln Pro Arg Ala Ala Ala Ala Ala Gln Pro
 35           40           45
Asp Gln Arg Gln Trp Glu Glu Thr Gln Glu Arg Gly His Leu Gln Pro
 50           55           60
Leu Ala Arg Gln Arg Arg Ser Ser Gly Leu Val Gln Asn Ile Asp Gln
 65           70           75           80
Leu Tyr Ser Gly Gly Gly Lys Val Gly Tyr Leu Val Tyr Ala Gly Gly
 85           90           95
Arg Arg Phe Leu Leu Asp Leu Glu Arg Asp Asp Thr Val Gly Ala Ala
100           105           110
Gly Gly Ile Val Thr Ala Gly Gly Leu Ser Ala Ser Ser Gly His Arg
115           120           125
Gly His Cys Phe Tyr Arg Gly Thr Val Asp Gly Ser Pro Arg Ser Leu
130           135           140
Ala Val Phe Asp Leu Cys Gly Gly Leu Asp Gly Phe Phe Ala Val Lys
145           150           155           160
His Ala Arg Tyr Thr Leu Arg Pro Leu Leu Arg Gly Ser Trp Ala Glu
165           170           175
Ser Glu Arg Val Tyr Gly Asp Gly Ser Ser Arg Ile Leu His Val Tyr
180           185           190
Thr Arg Glu Gly Phe Ser Phe Glu Ala Leu Pro Pro Arg Thr Ser Cys
195           200           205
Glu Thr Pro Ala Ser Pro Ser Gly Ala Gln Glu Ser Pro Ser Val His
210           215           220
Ser Ser Ser Arg Arg Arg Thr Glu Leu Ala Pro Gln Leu Leu Asp His
225           230           235           240
Ser Ala Phe Ser Pro Ala Gly Asn Ala Gly Pro Gln Thr Trp Trp Arg
245           250           255
Arg Arg Arg Arg Ser Ile Ser Arg Ala Arg Gln Val Glu Leu Leu Leu
260           265           270
Val Ala Asp Ser Ser Met Ala Lys Met Tyr Gly Arg Gly Leu Gln His
275           280           285
Tyr Leu Leu Thr Leu Ala Ser Ile Ala Asn Arg Leu Tyr Ser His Ala
290           295           300
Ser Ile Glu Asn His Ile Arg Leu Ala Val Val Lys Val Val Val Leu
305           310           315           320
Thr Asp Lys Ser Leu Glu Val Ser Lys Asn Ala Ala Thr Thr Leu Lys
325           330           335
Asn Phe Cys Lys Trp Gln His Gln His Asn Gln Leu Gly Asp Asp His
340           345           350
Glu Glu His Tyr Asp Ala Ala Ile Leu Phe Thr Arg Glu Asp Leu Cys
355           360           365
Gly His His Ser Cys Asp Thr Leu Gly Met Ala Asp Val Gly Thr Ile
370           375           380
Cys Ser Pro Glu Arg Ser Cys Ala Val Ile Glu Asp Asp Gly Leu His
385           390           395           400

```

Ala Ala Ph Thr Val Ala His Glu Ile Gly His Leu Leu Gly Leu Ser
 405 410 415
 His Asp Asp Ser Lys Phe Cys Glu Glu Asn Phe Gly Ser Thr Glu Asp
 420 425 430
 Lys Arg Leu Met Ser Ser Ile Leu Thr Ser Ile Asp Ala Ser Lys Pro
 435 440 445
 Trp Ser Lys Cys Thr Ser Ala Thr Ile Thr Glu Phe Leu Asp Asp Gly
 450 455 460
 His Gly Asn Cys Leu Leu Asp Val Pro Arg Lys Gln Ile Leu Gly Pro
 465 470 475 480
 Glu Glu Leu Pro Gly Gln Thr Tyr Asp Ala Thr Gln Gln Cys Asn Leu
 485 490 495
 Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly Met Asp Val Cys Ala
 500 505 510
 Arg Leu Trp Cys Ala Val Val Arg Gln Gly Gln Met Val Cys Leu Thr
 515 520 525
 Lys Lys Leu Pro Ala Val Glu Gly Thr Pro Cys Gly Lys Gly Arg Ile
 530 535 540
 Cys Leu Gln Gly Lys Cys Val Asp Lys Thr Lys Lys Tyr Tyr Ser
 545 550 555 560
 Thr Ser Ser His Gly Asn Trp Gly Ser Trp Gly Pro Trp Gly Gln Cys
 565 570 575
 Ser Arg Ser Cys Gly Gly Gly Val Gln Phe Ala Tyr Arg His Cys Asn
 580 585 590
 Asn Pro Ala Pro Arg Asn Ser Gly Arg Tyr Cys Thr Gly Lys Arg Ala
 595 600 605
 Ile Tyr Arg Ser Cys Ser Val Ile Pro Cys Pro Pro Asn Gly Lys Ser
 610 615 620
 Phe Arg His Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
 625 630 635 640
 Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
 645 650 655
 Leu Pro Ala Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
 660 665 670
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 675 680 685
 Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Arg Cys Val Arg Thr Gly
 690 695 700
 Cys Asp Gly Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
 705 710 715 720
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile Ile Gly Thr Phe Asn
 725 730 735
 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 740 745 750
 Thr His Ile Lys Val Arg Gln Phe Lys Ala Xaa Asp Gln Thr Arg Phe
 755 760 765
 Thr Ala Tyr Leu Ala Leu Lys Lys Lys Thr Gly Glu Tyr Leu Ile Asn
 770 775 780
 Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile Ile Asp Ile Asn Gly
 785 790 795 800
 Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg Asp Asp Phe Leu His
 805 810 815
 Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu Ile Val Gln Ile Leu
 820 825 830
 Ala Thr Asp Pro Thr Lys Ala Leu Asp Val Arg Tyr Ser Phe Phe Val

```
<210> 5
<211> 4067
<212> DNA
<213> Homo sapien
```

cactggcgga	gaaaaatcccc	tctctttttt	tctctctctt	tttttctttt	tgagacggaa	60
tctcactctt	tcaccagac	tggagggcag	cggcgagatc	tcggctcact	gcaacctcca	120
cctcccaggt	tcaagcaatt	ctcctgcctc	agccttccga	gtagctggga	ttacaggtgc	180
ccgccaccaac	gccagactaa	tttttgtatt	tttagtagag	acaggatttt	accatgttgg	240
ccatgctggt	ctcaaactcc	tgacctctgt	tgatccccct	gcttcagcct	ctcaaactgc	300
tgggattata	ggcatgagcc	actgcgcctg	gccaaacatc	cccttctaaa	ggcagtggtg	360
gtctccagca	ccaggggccat	acggctgcaa	cacccctaca	agtgcggggt	ctgccagaca	420
accacgacca	actagtccca	gataaccttg	aggcctgggc	actggctggg	ccccgagggc	480
tcttcccaaa	gcgtaccctg	gtcatctgga	agaggatcgg	agctggcctg	gtggtgacag	540
tggccttgct	tcctaggatg	gatggcagat	ggcaatgttc	ctgctggggc	tggttctctgc	600
tggttctggc	agttgtagct	ggggacacag	tgtcaaccgg	gtccacggag	aacagcccaa	660
catccataag	cctggagggg	ggcaccgacg	ccacggcctt	ctgggtgggg	gagtgagacca	720
atgtgacggc	gttttcccg	agttgcgggg	gtggggtgac	atcccaggag	cggcactgcc	780
tgcagcagag	gaggaagtcc	gtcccggggc	ccgggaacag	gacctgcacg	ggcacgtcca	840
agcggtagca	gctctgcaga	gtgcaggagt	gtccgcggga	cgggaggagc	ttccgcgagg	900
agcagtgcgt	ctccttcaac	tcccacgtgt	acaacgggcg	gacgcaccag	tggaagcctc	960
tgtacccgga	tgactatgtc	cacatctcca	gcaaaccctg	tgacctgcac	tgtaccaccc	1020
tggacggcca	ggcgagctc	atggtccccg	cccgcgacgg	gcactctgc	aagctcactg	1080
acctgcgagg	ggtttgcggt	tctggaaaat	gtgagcccat	cggctgtgac	ggggtgcttt	1140
tctccacca	cacactggac	aagtgtggca	tctgccaggg	ggacggtagc	agctgacccc	1200
acgtgacggg	caactatcgc	aaggggaatg	cccaccttgg	ttactctctg	gtgaccaca	1260
tcccggctgg	tgcccagac	atccagattg	tagagaggaa	gaagtccgct	gacgtgctag	1320
ctcttgcaga	tgaagctggc	tactactctt	tcaacggcaa	ctacaagggt	gacagcccca	1380
agaacttcaa	ctacgtctgc	acggtgtgtca	agtaccggcg	gcccatggat	gtctatgaga	1440
ccggaatcga	gtacatcggt	gcacaggggc	ccaccaacca	gggcctgaat	gtcatggtgt	1500
ggaaccagaa	cggcaaaagc	ccctccatca	ccttcgagta	cacgctgctg	cagccgccac	1560
acgagagccg	ccccagccc	atctactatg	gcttctccga	gagcgctgag	agccaggggc	1620
tggacggggc	cgggctgatg	ggcttcatcc	cgcacaacgg	ctccctctac	ggccaggcct	1680
cctcagagcg	gctgggcctg	gacaaccggc	tgttcggcca	ccggggcctg	gacatggagc	1740
tgcgccccag	ccaggccag	gagaccaacg	agggtgtcga	gcaggccggc	ggcggggcct	1800
gcgagggggc	ccccaggggc	aagggcttcc	gagaccgcaa	cgtcacgggg	actcctctca	1860
ccggggacaa	ggatgacgaa	gaggttgaca	cccacttcgc	ctcccaggag	ttcttctcgg	1920
ctaacgccat	ctctgaccag	ctgctgggcy	caggctctga	cttgaaggac	ttcaccccca	1980
atgagactgt	gaacagcatc	tttgacaggg	gcgccccagg	gagctccctg	gccgagagct	2040
tcttctgtgga	ttatgaggag	aacgaggggg	ctggccctta	cctgctcaac	gggttctacc	2100
tggagctgag	cagcgacagg	gttgccaaca	gctcctccga	ggccccattc	cccaacttta	2160
gcgaccgct	gctcacctcg	gccgggaaca	ggactcaca	ggccaggacc	aggccaagg	2220
cgcgcaagca	aggcgtgagt	cccgcggaca	tgtaccgggt	gaagctctcg	tcccacgagc	2280
cctgcagtgc	cacctgcacc	acaggggtca	tgtctgcgta	cgcctatgtg	gtccgctatg	2340
atggcgctga	ggtggatgac	agctactgtg	acgcctgac	ccgtcccag	actgtccagc	2400
agttctgcgc	tgggaggagg	tgccagccca	ggtgggagac	gagcagctgg	cgcgagtgtg	2460
cgcgcacctg	cagagagggc	taccagttcc	cgctctgtcg	ctgctggaag	atgctctcgc	2520
ccggcttcga	cgactccgtg	tacagcgacc	tgtgcgaggc	agccgaggcc	gtgcggcccc	2580

```

aggaacgcaa gacctgccgg aacccccgct gcggggcccca gtgggagatg tcggagtggg 2640
ccgagtgcac tgccaagtgt ggggagcgca gtgtggtgac cagggacatc cgctgctcgg 2700
aggatgagaa gctgtgtgac cccaacacca ggctgttagg ggagaagaac tgcacggggc 2760
cgccctgtga ccggcagtggt accgtctccg actggggacc gtgcagtgga agctgcgggc 2820
aaggccgcac catcaggcac gtgtactgca agaccagcga cggacgggta gtacctgagt 2880
cccagtgcc aatggagacc aagcctctgg ccattccacc ctgtggggac aaaaactgtc 2940
ccgcccactg gctggcccag gactgggagc ggtgcaacac cacctgcggg cgcggggtca 3000
agaagcggct ggtgctctgc atggagctgg ccaacgggaa gccgcagacg cgcagtggcc 3060
ccgagtgcgg gctcgccaag aagcctcccg aggagagcac gtgtttcgag agggcctgct 3120
tcaagtggta caccagcccc tggtcagagt gcaccaagac ctgcgggggtg ggcgtgagga 3180
tgcgagacgt caagtgtac caggggaccg acatcgctccg tggttgcgat ccgttggtga 3240
agcccgttg cagacaggcc tgtgatctgc agccctgccc caggagccc ccagatgaca 3300
gctgccagga ccagccaggc accaactgtg ccctggccat caaagtgaac ctctgcgggc 3360
actggtaacta cagcaaggcg tgctgcccgt cctgcaggcc ccccccactc taggccggc 3420
agctgcagcc ccttcagat gaagaccaag cgcccctcct ggggctgctg cagcttctgg 3480
ggcctccaca gacccccctc ctgcggggca cgctggccta agagacgtgg cactgagcct 3540
cggctgtcga gaggggactt cccacggccc gtggaccttt gtgctcctgg ggcagagcct 3600
ccggcaccca gtggcctccc ccagacagag ccaccctgc cgtgggaacc tgtccgtgtt 3660
cctgcgtgga tcctgtgttt gtggctccca ctcccagcc cccagcagc cccagccga 3720
ggggccagg gccacagcc agcgggtggag gtgtcttgct ccgggcccgt agcccacgcc 3780
ctctctgggt ggcagggcct tctgaaggaa acttgaggc gagcccaacg tgggtggggg 3840
ccttcctccc tcagaggcca tggggtgaga ggggctcagg cagccaagga ggccaggcg 3900
tgctccctct tatggagccc ctcccatgga gctctcttcc cgccgcactt tctaccccg 3960
gcagaggcgc ttgcccacgg gacgtttggg gatggacctc ggcccccgcc cctgcagtca 4020
gcgtcagtg tcactctacgt taataaagtg gtctatttta tggcggc 4067

```

<210> 6

<211> 951

<212> PRT

<213> Homo sapien

<400> 6

```

Met Asp Gly Arg Trp Gln Cys Ser Cys Trp Ala Trp Phe Leu Leu Val
1          5          10          15
Leu Ala Val Val Ala Gly Asp Thr Val Ser Thr Gly Ser Thr Asp Asn
20          25          30
Ser Pro Thr Ser Asn Ser Leu Glu Gly Gly Thr Asp Ala Thr Ala Phe
35          40          45
Trp Trp Gly Glu Trp Thr Lys Trp Thr Ala Phe Ser Arg Ser Cys Gly
50          55          60
Gly Gly Val Thr Ser Gln Glu Arg His Cys Leu Gln Gln Arg Arg Lys
65          70          75          80
Ser Val Pro Gly Pro Gly Asn Arg Thr Cys Thr Gly Thr Ser Lys Arg
85          90          95
Tyr Gln Leu Cys Arg Val Gln Glu Cys Pro Pro Asp Gly Arg Ser Phe
100          105          110
Arg Glu Glu Gln Cys Val Ser Phe Asn Ser His Val Tyr Asn Gly Arg
115          120          125
Thr His Gln Trp Lys Pro Leu Tyr Pro Asp Asp Tyr Val His Ile Ser
130          135          140
Ser Lys Pro Cys Asp Leu His Cys Thr Thr Val Asp Gly Gln Arg Gln
145          150          155          160
Leu Met Val Pro Ala Arg Asp Gly Thr Ser Cys Lys Leu Thr Asp Leu
165          170          175
Arg Gly Val Cys Val Ser Gly Lys Cys Glu Pro Ile Gly Cys Asp Gly

```

[illegible]

Arg Trp Glu Thr Ser Ser Trp Ser Glu Cys Ser Arg Thr Cys Gly Glu
 625 630 635 640
 Gly Tyr Gln Phe Arg Val Val Arg Cys Trp Lys Met Leu Ser Pro Gly
 645 650 655
 Phe Asp Ser Ser Val Tyr Ser Asp Leu Cys Glu Ala Ala Glu Ala Val
 660 665 670
 Arg Pro Glu Glu Arg Lys Thr Cys Arg Asn Pro Ala Cys Gly Pro Gln
 675 680 685
 Trp Glu Met Ser Glu Trp Ser Glu Cys Thr Ala Lys Cys Gly Glu Arg
 690 695 700
 Ser Val Val Thr Arg Asp Ile Arg Cys Ser Glu Asp Glu Lys Leu Cys
 705 710 715 720
 Asp Pro Asn Thr Arg Pro Val Gly Glu Lys Asn Cys Thr Gly Pro Pro
 725 730 735
 Cys Asp Arg Gln Trp Thr Val Ser Asp Trp Gly Pro Cys Ser Gly Ser
 740 745 750
 Cys Gly Gln Gly Arg Thr Ile Arg His Val Tyr Cys Lys Thr Ser Asp
 755 760 765
 Gly Arg Val Val Pro Glu Ser Gln Cys Gln Met Glu Thr Lys Pro Leu
 770 775 780
 Ala Ile His Pro Cys Gly Asp Lys Asn Cys Pro Ala His Trp Leu Ala
 785 790 795 800
 Gln Asp Trp Glu Arg Cys Asn Thr Thr Cys Gly Arg Gly Val Lys Lys
 805 810 815
 Arg Leu Val Leu Cys Met Glu Leu Ala Asn Gly Lys Pro Gln Thr Arg
 820 825 830
 Ser Gly Pro Glu Cys Gly Leu Ala Lys Lys Pro Pro Glu Glu Ser Thr
 835 840 845
 Cys Phe Glu Arg Pro Cys Phe Lys Trp Tyr Thr Ser Pro Trp Ser Glu
 850 855 860
 Cys Thr Lys Thr Cys Gly Val Gly Val Arg Met Arg Asp Val Lys Cys
 865 870 875 880
 Tyr Gln Gly Thr Asp Ile Val Arg Gly Cys Asp Pro Leu Val Lys Pro
 885 890 895
 Val Gly Arg Gln Ala Cys Asp Leu Gln Pro Cys Pro Thr Glu Pro Pro
 900 905 910
 Asp Asp Ser Cys Gln Asp Gln Pro Gly Thr Asn Cys Ala Leu Ala Ile
 915 920 925
 Lys Val Asn Leu Cys Gly His Trp Tyr Tyr Ser Lys Ala Cys Cys Arg
 930 935 940
 Ser Cys Arg Pro Pro His Ser
 945 950

<210> 7

<211> 5774

<212> DNA

<213> Homo sapien

<400> 7

gtcacttttg	ttgatagcag	ccgctctggt	agaggttagg	acttcagctg	atggacaagc	60
tggtaatgaa	gaaatggtgc	aaatagattt	accaataaag	agatatagag	agtatgagct	120
ggtgactcca	gtcagcacia	atctagaagg	acgctatctc	tcccatactc	tttctgcgag	180
tcacaaaaag	aggtcagcga	gggacgtgtc	ttccaaccct	gagcagttgt	tctttaacat	240
cacggcattt	ggaaaagatt	ttcatctgcg	actaaagccc	aacactcaac	tagtagctcc	300
tggggctggt	gtggagtggc	atgagacatc	tctggtgcct	gggaatataa	ccgatcccat	360

taacaacccat	caaccaggaa	gtgctacgta	tagaatccgg	aaaacagagc	ctttgcagac	420
taactgtgct	tatgttggtg	acatcggtga	cattccaggga	acctctgttg	ccatcagcaa	480
ctgtgatggt	ctggctggaa	tgataaaaag	tgataatgaa	gagtatattca	ttgaaccctt	540
ggaaagaggt	aaacagatgg	aggaagaaaa	aggaaggatt	catgttgtct	acaagagatc	600
agctgtagaa	caggctccca	tagacatgtc	caaagacttc	cactacagag	agtcggacct	660
ggaaggcctt	gatgatctag	gtactgttta	tggcaacatc	caccagcagc	tgaatgaaac	720
aatgagacgc	cgagacacg	cgggagaaaa	cgattacaat	atcgaggtag	tgctgggagt	780
ggatgactct	gtggtccgtt	tccatggcaa	agagcacgtc	caaaactacc	tcctgacctt	840
aatgaacatt	gtgaatgaaa	tttaccatga	tgagtccctc	ggagtgcata	taaatgtggt	900
cctggtgcgc	atgataatgc	tgggatatgc	aaagtccatc	agcctcatag	aaaggggaaa	960
cccatccaga	agcttgagga	atgtgtgtcg	ctgggctgct	caacagcaaa	gatctgatct	1020
caaccactct	gaaccaccatg	accatgcaat	ttttttaacc	aggcaagact	ttggacctgc	1080
tggaatgcaa	ggatatgtct	cagtcaccgg	catgtgtcat	ccagtggaga	gttgtacctt	1140
gaatcatgag	gatggttttt	catctgcttt	tgtagttagcc	catgaaacgg	gccatgtggt	1200
gggaatggag	catgatggac	aaggcaacag	gtgtggtgat	gagactgcta	tgggaagtgt	1260
catggctccc	ttggtacaag	cagcattcca	tcgttaccac	tgggtccgat	gcagtgggtca	1320
agaactgaaa	agatatatcc	attcctatga	ctgtctcctt	gatgacctt	ttgatcatga	1380
ttggcctaaa	ctcccagaac	ttcctggaat	caattattct	atggatgagc	aatgtcgttt	1440
tgattttggt	gttggtctata	aaatgtgcac	cgcgttccga	acctttgacc	catgtaaaca	1500
gctgtggtgt	agccatcctg	ataatcccta	cttttctaag	actaaaaagg	gacctccact	1560
tgatgggact	gaatgtgctg	ctggaaaaatg	gtgctataag	ggtcattgca	tgtggaagaa	1620
tgctaatacag	caaaaacaag	atggcaattg	ggggtcatgg	actaaatttg	gctcctgttc	1680
tcggacatgt	ggaactgggtg	ttcgtttcag	aacacgccag	tgcaataatc	ccatgcccat	1740
caatggtggt	caggattgtc	ctggtgttaa	ttttgagtac	cagctttgta	acacagaaga	1800
atgcaaaaaa	cactttgagg	acttcagagc	acagcagtg	cagcagcgaa	actcccactt	1860
tgaataccag	aataccaaac	accactgggt	gccatgatga	catcctgacc	ccaagaaaaag	1920
atgccacctt	tactgtcagt	ccaaggagac	tggagatggt	gcttacatga	aacaactggt	1980
gcatgatgga	acgcactggt	cttacaaga	tccatatagc	atatgtgtgc	gaggagagtg	2040
tgtgaaagtg	ggctgtgata	aagaaattgg	ttctaataag	gttgaggata	agtgtgggtg	2100
ctgtggagga	gataattccc	actgccgaac	cgtgaagggg	acattttacca	gaactcccag	2160
gaagcttggg	taccttaaga	tgtttgatat	accccctggg	gctagacatg	tgtaatcca	2220
agaagacgag	gcttctcctc	atattcttgc	tattaagaac	caggctacag	gccattatat	2280
tttaaatggc	aaagggggag	aagccaagtc	gcggaccttc	atagatcttg	gtgtggagtg	2340
ggattataac	attgaagatg	acattgaaag	tcttcacacc	gatggacctt	tacatgatcc	2400
tgttattgtt	ttgattatac	ctcaagaaaa	tgataccgcg	tctagcctga	catataagta	2460
catcatccat	gaagactctg	tacctacaat	caacagcaac	aatgtcatcc	aggaagaatt	2520
agatactttt	gagtgggctt	tgaagagctg	gtctcagggt	tccaaaccct	gtggtggagg	2580
tttcagtagc	actaaatatg	gatgccgtag	gaaaagtgat	aataaaatgg	tccatcgag	2640
cttctgtgag	gccaacaaaa	agccgaaacc	tattagacga	atgtgcaata	ttcaagagtg	2700
tacacatcca	ctctgggtag	cagaagaatg	ggaacactgc	acaaaaacct	gtggaagtct	2760
tggctatcag	cttcgcactg	tacgtgcctt	tcagccactc	cttgatggca	ccaaccgctc	2820
tgtgcacagc	aaatactgca	tgggtgaccg	tcccagagagc	cgccggccct	gtaacagagt	2880
gccctgccct	gcacagtgga	aaacaggacc	ctggagtggg	tgttcagtga	cctgcggtga	2940
aggaacggag	gtgaggcagg	tcctctgcag	ggctggggac	cactgtgatg	gtgaaaagcc	3000
tgagtccgtc	agagcctgtc	aactgcctcc	ttgtaatgat	gaaccatggt	tgggagacaa	3060
gtccatattc	tgtcaaatgg	aagtgttggc	acgatactgc	tccataccag	gttataacaa	3120
gttatgttgt	gagtcctgca	gcaagcgcag	tagcaccttg	ccaccaccat	accttctaga	3180
agctgctgaa	actcatgatg	atgtcatctc	taaccctagt	gacctcccta	gatctctagt	3240
gatgcctaca	tctttgggtc	cttatcatte	agagacccct	gcaaagaaga	tgtctttgag	3300
tagcatctct	tcagtgggag	gtccaaatgc	atatgtgtgt	ttcaggccaa	acagttaaacc	3360
tgatggtgct	aatttacgcc	agaggagtgc	tcagcaagca	ggaagtgaaga	ctgtgagact	3420
ggtcaccgta	cattctccc	caccacccaa	gagggctccac	ctcagttcag	cttcacaaat	3480
ggctgctgct	tccttctttg	cagccagtga	ttcaataggt	gcttcttctc	aggcaagaac	3540
ctcaaagaaa	gatggaaaga	tcattgacaa	cagacgtccg	acaagatcat	ccaccttaga	3600
aagatgagaa	agtgaaccaa	aaaggctaga	aaccagagga	aaacctggac	aacctctctc	3660

```

ttcccatggt gcatatgctt gtttaaagtg gaaatctcta tagatcgtca gctcatttta 3720
tctgtaattg gaagaacaga aagtgcctggc tcactttcta gttgctttca tcctcctttt 3780
gttctgcatt gactcattta ccagaattca ttggaagaaa tcaccaaaga ttattacaaa 3840
agaaaaatat gttgctaaga ttgtgttggt cgctctctga agcagaaaaag ggactgggac 3900
caattgtgca tatcagctga ctttttggtt gttttagaaa agttacagta aaaattaaaa 3960
agagatacca atggttttaca ctttaacaag aaatttttgg tatggaacaa agaattctta 4020
gacttgtatt cctatattatc tatattagaa atattgtatg agcaaatttg cagctgttgt 4080
gtaaaactg tatattgcaa aaatcagtat tattttaaga gatgtgttct caaatgattg 4140
tttactatat tacattttctg gatgttctag gtgcctgtcg ttgagtattg ccttgtttga 4200
cattctatag gtttaattttc aaagcagagt attacaaaag agaagttaga attacagcta 4260
ctgacaatat aaagggtttt gttgaatcaa caatgtgata cgtaaattat agaaaaagaa 4320
aagaaacaca aaagctatag atatacagat atcagcttac ctattgcctt ctatacttat 4380
aatttaaagg attgggtgtct tagtacactt gtggtcacag ggatcaacga atagtaaata 4440
atgaactcgt gcaagacaaa actgaaaccc tctttccagg acctcagtag gcaccgttga 4500
gggtgccttt gtttttggtg gtgtgtgttc ttttttaatt ttgcattgt tgacagatac 4560
aaacagttat actcaatgta ctgtaataat cgcaaaggaa aaagttttgg gataacttat 4620
ttgtatgttg gtagctgaga aaaatatcat cagtctagaa ttgatatttg agtatagtag 4680
agctttgggg ctttgaaggc aggttcaaga aagcatatgt cgatggttga gatatttatt 4740
ttccatatgg ttcatgttca aatgttcaca accacaatgc atctgactgc aataatgtgc 4800
taataattta tgtcagtagt caccctgctc acagcaaagc cagaaatgct ctctccaggg 4860
agtagatgta aagtacttgt acatagaatt cagaactgaa gatatttatt aaaagttgat 4920
tttttttct tgatagtatt tttatgtact aaatatttac actaatatca attacatatt 4980
ttggtaaaact agagagacat aattagagat gcattgctttg ttctgtgcat agagaccttt 5040
aagcaacta ctacagccaa ctcaaaagct aaaactgaac aaatttgatg ttatgcaaac 5100
atcttgcat tttagtagtt gatattaagt tgatgacttg tttcccttca aggaaacatt 5160
aaattgtatg gactcagcta gctgttcaat gaaattgtga attagaaaca tttttaaaag 5220
ttttgaaag agataagtgc atcatgaatt acatgtacat gagaggagat agtgatatca 5280
gcataatgat tttgaggtca gtacctgagc tgtctaaaaa tatattatac aaactaaaat 5340
gtagatgaat taacctctca aagcacagaa tgtgcaagaa cttttgcatt ttaatcgttg 5400
taaactaaca gcttaaacta ttgactctat acctctaaag aattgctgct actttgtgca 5460
agaactttga aggtcaaatt aggcaaattc catagatgaa aacaatccct aagccttaag 5520
tctttttttt ttccataaaa ttcccataga ataaaattct ctctagttaa cttgtgtgtg 5580
catacatctc atccacaggg gaagataaag atggtcacac aaacagtttc cataaagatg 5640
tacatattca ttatacttct gacctttggg ctttcttttc tactaagcta aaaattcctt 5700
tttatcaaag tgtacactac tgatgctgtt tgttgtactg agagcacgta ccaataaaaa 5760
tgtaaacaaa atat 5774

```

<210> 8

<211> 1201

<212> PRT

<213> Homo sapien

<400> 8

```

Ser Leu Trp Leu Ile Ala Ala Ala Leu Val Glu Val Arg Thr Ser Ala
1           5           10          15
Asp Gly Gln Ala Gly Asn Glu Glu Met Val Gln Ile Asp Leu Pro Ile
20          25          30
Lys Arg Tyr Arg Glu Tyr Glu Leu Val Thr Pro Val Ser Thr Asn Leu
35          40          45
Glu Gly Arg Tyr Leu Ser His Thr Leu Ser Ala Ser His Lys Lys Arg
50          55          60
Ser Ala Arg Asp Val Ser Ser Asn Pro Glu Gln Leu Phe Phe Asn Ile
65          70          75          80
Thr Ala Phe Gly Lys Asp Phe His Leu Arg Leu Lys Pro Asn Thr Gln
85          90          95

```

Leu	Val	Ala	Pro	Gly	Ala	Val	Val	Glu	Trp	His	Glu	Thr	Ser	Leu	Val
			100					105					110		
Pro	Gly	Asn	Ile	Thr	Asp	Pro	Ile	Asn	Asn	His	Gln	Pro	Gly	Ser	Ala
		115					120					125			
Thr	Tyr	Arg	Ile	Arg	Lys	Thr	Glu	Pro	Leu	Gln	Thr	Asn	Cys	Ala	Tyr
	130				135						140				
Val	Gly	Asp	Ile	Val	Asp	Ile	Pro	Gly	Thr	Ser	Val	Ala	Ile	Ser	Asn
145					150					155					160
Cys	Asp	Gly	Leu	Ala	Gly	Met	Ile	Lys	Ser	Asp	Asn	Glu	Glu	Tyr	Phe
				165					170					175	
Ile	Glu	Pro	Leu	Glu	Arg	Gly	Lys	Gln	Met	Glu	Glu	Glu	Lys	Gly	Arg
			180					185					190		
Ile	His	Val	Val	Tyr	Lys	Arg	Ser	Ala	Val	Glu	Gln	Ala	Pro	Ile	Asp
		195					200					205			
Met	Ser	Lys	Asp	Phe	His	Tyr	Arg	Glu	Ser	Asp	Leu	Glu	Gly	Leu	Asp
	210					215					220				
Asp	Leu	Gly	Thr	Val	Tyr	Gly	Asn	Ile	His	Gln	Gln	Leu	Asn	Glu	Thr
225					230					235					240
Met	Arg	Arg	Arg	Arg	His	Ala	Gly	Glu	Asn	Asp	Tyr	Asn	Ile	Glu	Val
				245					250					255	
Leu	Leu	Gly	Val	Asp	Asp	Ser	Val	Val	Arg	Phe	His	Gly	Lys	Glu	His
			260					265					270		
Val	Gln	Asn	Tyr	Leu	Leu	Thr	Leu	Met	Asn	Ile	Val	Asn	Glu	Ile	Tyr
	275						280					285			
His	Asp	Glu	Ser	Leu	Gly	Val	His	Ile	Asn	Val	Val	Leu	Val	Arg	Met
	290				295					300					
Ile	Met	Leu	Gly	Tyr	Ala	Lys	Ser	Ile	Ser	Leu	Ile	Glu	Arg	Gly	Asn
305					310					315					320
Pro	Ser	Arg	Ser	Leu	Glu	Asn	Val	Cys	Arg	Trp	Ala	Ser	Gln	Gln	Gln
			325					330					335		
Arg	Ser	Asp	Leu	Asn	His	Ser	Glu	His	His	Asp	His	Ala	Ile	Phe	Leu
			340					345					350		
Thr	Arg	Gln	Asp	Phe	Gly	Pro	Ala	Gly	Met	Gln	Gly	Tyr	Ala	Pro	Val
		355					360					365			
Thr	Gly	Met	Cys	His	Pro	Val	Arg	Ser	Cys	Thr	Leu	Asn	His	Glu	Asp
	370					375					380				
Gly	Phe	Ser	Ser	Ala	Phe	Val	Val	Ala	His	Glu	Thr	Gly	His	Val	Leu
385					390					395					400
Gly	Met	Glu	His	Asp	Gly	Gln	Gly	Asn	Arg	Cys	Gly	Asp	Glu	Thr	Ala
			405					410					415		
Met	Gly	Ser	Val	Met	Ala	Pro	Leu	Val	Gln	Ala	Ala	Phe	His	Arg	Tyr
			420					425					430		
His	Trp	Ser	Arg	Cys	Ser	Gly	Gln	Glu	Leu	Lys	Arg	Tyr	Ile	His	Ser
	435						440					445			
Tyr	Asp	Cys	Leu	Leu	Asp	Asp	Pro	Phe	Asp	His	Asp	Trp	Pro	Lys	Leu
	450					455				460					
Pro	Glu	Leu	Pro	Gly	Ile	Asn	Tyr	Ser	Met	Asp	Glu	Gln	Cys	Arg	Phe
465					470					475					480
Asp	Phe	Gly	Val	Gly	Tyr	Lys	Met	Cys	Thr	Ala	Phe	Arg	Thr	Phe	Asp
			485						490					495	
Pro	Cys	Lys	Gln	Leu	Trp	Cys	Ser	His	Pro	Asp	Asn	Pro	Tyr	Phe	Cys
			500					505					510		
Lys	Thr	Lys	Lys	Gly	Pro	Pro	Leu	Asp	Gly	Thr	Glu	Cys	Ala	Ala	Gly
		515					520					525			
Lys	Trp	Cys	Tyr	Lys	Gly	His	Cys	Met	Trp	Lys	Asn	Ala	Asn	Gln	Gln

530		535		540
Lys Gln Asp Gly Asn Trp Gly Ser Trp Thr Lys Phe Gly Ser Cys Ser				
545		550		555
Arg Thr Cys Gly Thr Gly Val Arg Phe Arg Thr Arg Gln Cys Asn Asn				560
	565		570	575
Pro Met Pro Ile Asn Gly Gly Gln Asp Cys Pro Gly Val Asn Phe Glu				
	580	585		590
Tyr Gln Leu Cys Asn Thr Glu Glu Cys Gln Lys His Phe Glu Asp Phe				
	595	600		605
Arg Ala Gln Gln Cys Gln Gln Arg Asn Ser His Phe Glu Tyr Gln Asn				
	610	615		620
Thr Lys His His Trp Leu Pro Tyr Glu His Pro Asp Pro Lys Lys Arg				
625		630		635
Cys His Leu Tyr Cys Gln Ser Lys Glu Thr Gly Asp Val Ala Tyr Met				
	645		650	655
Lys Gln Leu Val His Asp Gly Thr His Cys Ser Tyr Lys Asp Pro Tyr				
	660	665		670
Ser Ile Cys Val Arg Gly Glu Cys Val Lys Val Gly Cys Asp Lys Glu				
	675	680		685
Ile Gly Ser Asn Lys Val Glu Asp Lys Cys Gly Val Cys Gly Gly Asp				
	690	695		700
Asn Ser His Cys Arg Thr Val Lys Gly Thr Phe Thr Arg Thr Pro Arg				
705		710		715
Lys Leu Gly Tyr Leu Lys Met Phe Asp Ile Pro Pro Gly Ala Arg His				
	725		730	735
Val Leu Ile Gln Glu Asp Glu Ala Ser Pro His Ile Leu Ala Ile Lys				
	740	745		750
Asn Gln Ala Thr Gly His Tyr Ile Leu Asn Gly Lys Gly Glu Glu Ala				
	755	760		765
Lys Ser Arg Thr Phe Ile Asp Leu Gly Val Glu Trp Asp Tyr Asn Ile				
	770	775		780
Glu Asp Asp Ile Glu Ser Leu His Thr Asp Gly Pro Leu His Asp Pro				
785		790		795
Val Ile Val Leu Ile Ile Pro Gln Glu Asn Asp Thr Arg Ser Ser Leu				
	805		810	815
Thr Tyr Lys Tyr Ile Ile His Glu Asp Ser Val Pro Thr Ile Asn Ser				
	820	825		830
Asn Asn Val Ile Gln Glu Glu Leu Asp Thr Phe Glu Trp Ala Leu Lys				
	835	840		845
Ser Trp Ser Gln Val Ser Lys Pro Cys Gly Gly Gly Phe Gln Tyr Thr				
	850	855		860
Lys Tyr Gly Cys Arg Arg Lys Ser Asp Asn Lys Met Val His Arg Ser				
865		870		875
Phe Cys Glu Ala Asn Lys Lys Pro Lys Pro Ile Arg Arg Met Cys Asn				
	885	890		895
Ile Gln Glu Cys Thr His Pro Leu Trp Val Ala Glu Glu Trp Glu His				
	900	905		910
Cys Thr Lys Thr Cys Gly Ser Ser Gly Tyr Gln Leu Arg Thr Val Arg				
	915	920		925
Cys Leu Gln Pro Leu Leu Asp Gly Thr Asn Arg Ser Val His Ser Lys				
	930	935		940
Tyr Cys Met Gly Asp Arg Pro Glu Ser Arg Arg Pro Cys Asn Arg Val				
945		950		955
Pro Cys Pro Ala Gln Trp Lys Thr Gly Pro Trp Ser Glu Cys Ser Val				
	965	970		975

Thr Cys Gly Glu Gly Thr Glu Val Arg Gln Val L u Cys Arg Ala Gly
 980 985 990
 Asp His Cys Asp Gly Glu Lys Pro Glu Ser Val Arg Ala Cys Gln Leu
 995 1000 1005
 Pro Pro Cys Asn Asp Glu Pro Cys Leu Gly Asp Lys Ser Ile Phe Cys
 1010 1015 1020
 Gln Met Glu Val Leu Ala Arg Tyr Cys Ser Ile Pro Gly Tyr Asn Lys
 1025 1030 1035 1040
 Leu Cys Cys Glu Ser Cys Ser Lys Arg Ser Ser Thr Leu Pro Pro Pro
 1045 1050 1055
 Tyr Leu Leu Glu Ala Ala Glu Thr His Asp Asp Val Ile Ser Asn Pro
 1060 1065 1070
 Ser Asp Leu Pro Arg Ser Leu Val Met Pro Thr Ser Leu Val Pro Tyr
 1075 1080 1085
 His Ser Glu Thr Pro Ala Lys Lys Met Ser Leu Ser Ser Ile Ser Ser
 1090 1095 1100
 Val Gly Gly Pro Asn Ala Tyr Ala Ala Phe Arg Pro Asn Ser Lys Pro
 1105 1110 1115 1120
 Asp Gly Ala Asn Leu Arg Gln Arg Ser Ala Gln Gln Ala Gly Ser Lys
 1125 1130 1135
 Thr Val Arg Leu Val Thr Val Pro Ser Ser Pro Pro Thr Lys Arg Val
 1140 1145 1150
 His Leu Ser Ser Ala Ser Gln Met Ala Ala Ala Ser Phe Phe Ala Ala
 1155 1160 1165
 Ser Asp Ser Ile Gly Ala Ser Ser Gln Ala Arg Thr Ser Lys Lys Asp
 1170 1175 1180
 Gly Lys Ile Ile Asp Asn Arg Arg Pro Thr Arg Ser Ser Thr Leu Glu
 1185 1190 1195 1200
 Arg

<210> 9
 <211> 2868
 <212> DNA
 <213> Homo sapien

<400> 9
 ggaattcgcg gccgcgtcga cgtcaataacc aactccgagc acacggccgt catcagcctc 60
 tgctcaggaa tgctgggcac attccgggtct catgatgggg attattttat tgaaccacta 120
 cagtctatgg atgaacaaga agatgaagag gaacaaaaca aacccacat catttatagg 180
 cgcagcggcc cccagagaga gccctcaaca ggaaggcatg catgtgacac ctcagaacac 240
 aaaaatagga acagtaaaga caagaagaaa accagagcaa gaaaatgggg agaaaggatt 300
 aacctggctg gtgacgtagc agcattaaac agcggcttag caacagaggc attttctgct 360
 tatggtaata agacggacaa cacaagagaa aagaggaccc acagaaggac aaaacgtttt 420
 ttatcctatc cacggtttgt agaagtcttg gtggtggcag acaacagaat ggtttcatac 480
 catggagaaa accttcaaca ctatatatta actttaatgt caattgatgg gccttccata 540
 tcttttaatg ctcagacaac attaaaaaac ctttgccagt ggcagcattc gaagaacagt 600
 ccagggtgaa tccatcatga tactgctggt ctcttaacaa gacaggatat ctgcagagct 660
 cacgacaaat gtgatacctt aggcctggct gaactgggaa ccatttgtga tccctataga 720
 agctgttcta ttagtgaaga tagtggattg agtacagctt ttacgatcgc ccatgagctg 780
 ggccatgtgt ttaacatgcc tcatgatgac aacaacaaat gtaaagaaga aggagttaag 840
 agtccccagc atgtcatggc tccaacactg aacttctaca ccaaccctg gatgtggtca 900
 aagtgtagtc gaaaatatat cactgagttt ttagacactg gttatggcga gtgtttgctt 960
 aacgaacctg aatccagacc ctaccctttg cctgtccaac tgccaggcat cctttacaac 1020
 gtgaataaac aatgtgaatt gatttttggg ccagggttctc aggtgtgccc atatatgatg 1080

```

cagtgcagac ggctctgggtg caataacgtc aatggagtag acaaaggctg ccggactcag 1140
cacacaccct gggccgatgg gacggagtag gagcctggaa agcactgcaa gtatggattt 1200
tgtgttccca aagaaatgga tgtccccgtg acagatggat cctggggaag ttggagtccc 1260
tttggaaacct gctccagaac atgtggaggg ggcatacaaa cagccattcg agagtgaac 1320
agaccagaac caaaaaatgg tggaaaatac tgtgtaggac gtagaatgaa atttaagtcc 1380
tgcaacacgg agccatgtct caagcagaag cgagacttcc gagatgaaca gtgtgtcac 1440
tttgacggga agcattttta catcaacggt ctgcttccca atgtgcgctg ggtccctaaa 1500
tacagtggaa ttctgatgaa ggaccggtgc aagttgttct gcagagtggc agggaaacaca 1560
gcctactatc agcttcgaga cagagtgata gatggaaactc cttgtggcca ggacacaaat 1620
gatattctgtg tccagggcct ttgccggcaa gctggatgcg atcatgtttt aaactcaaaa 1680
gcccggagag ataaatgtgg ggtttgtggg ggcgataatt cttcatgcaa aacagtggca 1740
ggaacattta atacagtaca ttatggttac aatactgtgg tccgaattcc agctggtgct 1800
accaatattg atgtgcggca gcacagtttc tcaggggaaa cagacgatga caactactta 1860
gctttatcaa gcagtaaagg tgaattcttg ctaaaggaa actttgttgt cacaatggcc 1920
aaaagggaaa ttgcgattgg gaatgctgtg gtagagtaca gtgggtccga gactgccgta 1980
gaaagaatta actcaacaga tcgcattgag caagaacttt tgcttcaggt tttgtcgggtg 2040
ggaaagttgt acaaccccgga tgtacgctat tctttcaata ttccaattga agataaacct 2100
cagcagtttt actggaacag tcatgggcca tggcaagcat gcagtaaacc ctgccaaggg 2160
gaacggaaac gaaaacttgt ttgcaccagg gaatctgac agcttactgt ttctgatcaa 2220
agatgcgacg ggctgccccca gcctggacac attactgaac cctgtggtac agactgtgac 2280
ctgaggtggc atgttgccag caggagtga ttagtgccc agtgtggtt gggttaccgc 2340
acattggaca tctactgtgc caaatatagc aggtggatg ggaagactga gaaggtgat 2400
gatgggtttt gcagcagcca tcccaaacca agcaaccgtg aaaaatgctc aggggaatgt 2460
aacacgggtg gctggcgcta ttctgcctgg actgaatgtt caaaaagctg tgacggtggg 2520
accagagga gaagggctat ttgtgtcaat acccgaaatg atgtactgga tgacagcaaa 2580
tgacacacatc aagagaaagt taccattcag aggtgcagt agttccctt tccacagtgg 2640
aaatctggag actggtcaga gtgcttggtc acctgtggaa aagggcataa gcaccgccag 2700
gtctggtgtc agtttgggtga agatcgatta aatgatagaa tgtgtgaccc agaggtcgac 2760
gcggccgcga attccgcga tactgacggg ctccaggagt cgtcgccacc aatccccata 2820
tggaaccct cgatattcag ccatgtgcct tcaagccgaa ttccaggb 2868

```

<210> 10
 <211> 958
 <212> PRT
 <213> Homo sapien

```

<400> 10
Gly Ile Arg Gly Arg Val Asp Val Asn Thr Asn Ser Glu His Thr Ala
1      5      10      15
Val Ile Ser Leu Cys Ser Gly Met Leu Gly Thr Phe Arg Ser His Asp
20     25     30
Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp Glu Gln Glu Asp
35     40     45
Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
50     55     60
Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
65     70     75     80
Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
85     90     95
Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
100    105    110
Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
115    120    125
Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
130    135    140

```

Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser Tyr
 145 150 155 160
 His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Asp
 165 170 175
 Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys
 180 185 190
 Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
 195 200 205
 Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys
 210 215 220
 Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg
 225 230 235 240
 Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile
 245 250 255
 Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn
 260 265 270
 Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro
 275 280 285
 Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg
 290 295 300
 Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu
 305 310 315 320
 Asn Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly
 325 330 335
 Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
 340 345 350
 Ser Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn
 355 360 365
 Asn Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp
 370 375 380
 Ala Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe
 385 390 395 400
 Cys Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly
 405 410 415
 Ser Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Ile
 420 425 430
 Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly
 435 440 445
 Lys Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu
 450 455 460
 Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
 465 470 475 480
 Phe Asp Gly Lys His Phe Asn Ile Asn Gly Leu Leu Pro Asn Val Arg
 485 490 495
 Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu
 500 505 510
 Phe Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg
 515 520 525
 Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 530 535 540
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 545 550 555 560
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 565 570 575
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr

			580					585					590		
Val	Val	Arg	Ile	Pro	Ala	Gly	Ala	Thr	Asn	Ile	Asp	Val	Arg	Gln	His
		595					600					605			
Ser	Phe	Ser	Gly	Glu	Thr	Asp	Asp	Asp	Asn	Tyr	Leu	Ala	Leu	Ser	Ser
	610					615					620				
Ser	Lys	Gly	Glu	Phe	Leu	Asn	Gly	Asn	Phe	Val	Val	Thr	Met	Ala	
625				630					635					640	
Lys	Arg	Glu	Ile	Arg	Ile	Gly	Asn	Ala	Val	Val	Glu	Tyr	Ser	Gly	Ser
				645					650					655	
Glu	Thr	Ala	Val	Glu	Arg	Ile	Asn	Ser	Thr	Asp	Arg	Ile	Glu	Gln	Glu
			660					665					670		
Leu	Leu	Leu	Gln	Val	Leu	Ser	Val	Gly	Lys	Leu	Tyr	Asn	Pro	Asp	Val
		675					680					685			
Arg	Tyr	Ser	Phe	Asn	Ile	Pro	Ile	Glu	Asp	Lys	Pro	Gln	Gln	Phe	Tyr
	690					695					700				
Trp	Asn	Ser	His	Gly	Pro	Trp	Gln	Ala	Cys	Ser	Lys	Pro	Cys	Gln	Gly
705				710						715				720	
Glu	Arg	Lys	Arg	Lys	Leu	Val	Cys	Thr	Arg	Glu	Ser	Asp	Gln	Leu	Thr
				725					730					735	
Val	Ser	Asp	Gln	Arg	Cys	Asp	Arg	Leu	Pro	Gln	Pro	Gly	His	Ile	Thr
			740					745					750		
Glu	Pro	Cys	Gly	Thr	Asp	Cys	Asp	Leu	Arg	Trp	His	Val	Ala	Ser	Arg
		755					760					765			
Ser	Glu	Cys	Ser	Ala	Gln	Cys	Gly	Leu	Gly	Tyr	Arg	Thr	Leu	Asp	Ile
	770					775					780				
Tyr	Cys	Ala	Lys	Tyr	Ser	Arg	Leu	Asp	Gly	Lys	Thr	Glu	Lys	Val	Asp
785					790					795				800	
Asp	Gly	Phe	Cys	Ser	His	Pro	Lys	Pro	Ser	Asn	Arg	Glu	Lys	Cys	
				805					810					815	
Ser	Gly	Glu	Cys	Asn	Thr	Gly	Gly	Trp	Arg	Tyr	Ser	Ala	Trp	Thr	Glu
			820					825					830		
Cys	Ser	Lys	Ser	Cys	Asp	Gly	Gly	Thr	Gln	Arg	Arg	Arg	Ala	Ile	Cys
		835					840					845			
Val	Asn	Thr	Arg	Asn	Asp	Val	Leu	Asp	Asp	Ser	Lys	Cys	Thr	His	Gln
	850					855					860				
Glu	Lys	Val	Thr	Ile	Gln	Arg	Cys	Ser	Glu	Phe	Pro	Cys	Pro	Gln	Trp
865					870					875				880	
Lys	Ser	Gly	Asp	Trp	Ser	Glu	Cys	Leu	Val	Thr	Cys	Gly	Lys	Gly	His
				885					890					895	
Lys	His	Arg	Gln	Val	Trp	Cys	Gln	Phe	Gly	Glu	Asp	Arg	Leu	Asn	Asp
			900					905					910		
Arg	Met	Cys	Asp	Pro	Glu	Val	Asp	Ala	Ala	Ala	Asn	Ser	Ala	Asp	Thr
		915					920					925			
Asp	Gly	Leu	Gln	Glu	Ser	Ser	Pro	Pro	Ile	Pro	Ile	Trp	Lys	Pro	

```
<210> 11
<211> 4303
<212> DNA
<213> Homo sapien
```

<400> 11

cacatatgca cgagagagac agaggaggaa agagacagag acaaaggcac agcggaagaa

ggcagagaca	gggcaggcac	agaagcggcc	cagacagagt	cctacagagg	gagaggccag	120
agaagctgca	gaagacacag	gcagggagag	acaaagatcc	aggaaaggag	ggctcaggag	180
gagagtttgg	agaagccaga	cccctgggca	cctctcccaa	gcccaaggac	taagttttct	240
ccatttcctt	taacggctct	cagcccttct	gaaaactttg	cctctgacct	tggcaggagt	300
ccaagccccc	aggctacaga	gaggagcttt	ccaaagctag	ggtgtggagg	acttgggtgcc	360
ctagacggcc	tcagtccctc	ccagctgcag	taccagtgcc	atgtcccaga	caggctcgca	420
tcccgggaag	ggcttggcag	ggcgctggct	gtggggagcc	caaccctgcc	tcctgtctcc	480
cattgtgccc	ctctcctggc	tgggtgtggc	gcttctgcta	ctgctggcct	ctctcctgcc	540
ctcagccccc	ctggccagcc	ccctcccccg	ggaggaggag	atcgtgtttc	cagagaagct	600
caacggcagc	gtcctgcctg	gctcggggcac	ccctgccagg	ctgttgtgcc	gcttgcaggc	660
ctttggggag	acgctgctac	tagagctgga	gcaggactcc	ggtgtgcagg	tcgaggggct	720
gacagtgcag	tacctggggc	aggcgccctga	gctgctgggt	ggagcagagc	ctggcaccta	780
cctgactggc	accatcaatg	gagatccgga	gtcgggtggca	tctctgcact	gggatggggg	840
agccctgtta	ggcgtgttac	aatatcgggg	ggctgaactc	cacctccagc	ccctggaggg	900
aggcacccct	aactctgctg	ggggacctgg	ggctcacatc	ctacgcggga	agagtccctgc	960
cagcgggtcaa	ggtcccatgt	gcaacgtcaa	ggctcctctt	ggaagcccca	gccccagacc	1020
ccgaagagcc	aagcgctttg	cttcactgag	tagattttgt	gagacactgg	tgggtggcaga	1080
tgacaagatg	gcccatttcc	acggtgcggg	gctaaagcgc	tacctgctaa	cagtgatggc	1140
agcagcagcc	aaggccttca	agcacccaag	catccgcaat	cctgtcagct	tgggtgtgac	1200
tcggctagtg	atcctggggg	caggcgagga	ggggcccca	gtggggccca	gtgctgcca	1260
gacctgctgc	agcttctgtg	cctggcagcg	gggctcaac	acccctgagg	actcggaccc	1320
tgaccacttt	gacacagcca	ttctgtttac	ccgtcaggac	ctgtgtggag	tctccacttg	1380
cgacacgctg	ggtatggctg	atgtgggcac	cgctctgtac	ccggctcgga	gctgtgccat	1440
tgtggaggat	gatgggctcc	agtcagcctt	cactgtgtgt	catgaactgg	gtcatgtctt	1500
caacatgctc	catgacaact	ccaagccatg	catcagtttg	aatgggcctt	tgagcacctc	1560
tcgccatgct	atggcccttg	tgatggctca	tgtggatcct	gaggagccct	ggtccccctg	1620
cagtgcctgc	ttcatcactg	acttcctgga	caatggctat	gggcactgtc	tcttagacaa	1680
accagaggct	ccattgcatc	tgccctgtgac	tttccctggc	aaggactatg	atgctgaccg	1740
ccagtgcag	ctgaccttgc	ggccccgactc	acgccattgt	ccacagctgc	cgccgccttg	1800
tgctgccttc	tgggtgctctg	gccacctcaa	tggccatgcc	atgtgccaga	ccaaacactc	1860
ggcctggggc	gatggcacac	cctgcgggcc	cgcacaggcc	tgcatgggtg	gtcgtgtcct	1920
ccacatggac	cagctccagg	acttcaatat	tccacaggct	ggtgggtggg	gtccttgggg	1980
accatggggg	gactgtcttc	ggacctgtgg	gggtgtgtgc	cagttctcct	cccagagactg	2040
cacgaggcct	gtcccccgga	atgggtggcaa	gtactgtgag	ggccgcgcta	cccgttccg	2100
ctcctgcaac	actgaggact	gccccactgg	ctcagccctg	accttccgcg	aggagcagtg	2160
tgctgcctac	aaccaccgca	ccgacctctt	caagagcttc	ccaggggcca	tggactgggt	2220
tctcgtctac	acaggcgtgg	ccccccagga	ccagtgcaaa	ctcacctgcc	aggccccggc	2280
actgggctac	tactatgtgc	tggagccacg	ggtggtagat	gggacccctt	gttccccgga	2340
cagctcctcg	gtctgtgtcc	agggccgatg	catccatgct	ggctgtgatc	gcatcattgg	2400
ctccaagaag	aagtttgaca	agtgcattgg	gtgcggaggg	gacggttctg	gttgacgcaa	2460
gcagtcaggc	tccttcagga	aattcaggta	cggatacaac	aatgtgggtca	ctatccccgc	2520
ggggggccacc	cacattcttg	tccggcagca	gggaaaccc	ggccaccgga	gcattctactt	2580
ggccctgaag	ctgccagatg	gctcctatgc	cctcaatgg	gaatacacgc	tgatgccctc	2640
ccccacagat	gtgggtactgc	ctggggcag	cagcttgccg	tacagcgggg	ccactgcagc	2700
ctcagagaca	ctgtcaggcc	atggggcact	ggcccagcct	ttgacactgc	aagtccctagt	2760
ggctggcaac	ccccaggaca	cacgcctccg	atacagcttc	ttcgtgcccc	ggccgacccc	2820
ttcaacgcca	cgccccactc	cccaggactg	gctgcaccga	agagcacaga	ttctggagat	2880
ccttcggcgg	cgccccctggg	cgggcaggaa	ataacctcac	tatcccggct	gccctttctg	2940
ggcaccgggg	cctcggaactt	agctgggaga	aagagagagc	ttctgttgct	gcctcatgct	3000
aagactcagt	ggggaggggc	tgtgggcgtg	agacctgccc	ctcctctctg	ccctaagtgc	3060
caggctggcc	ctgccctggg	ttcctgccct	gggaggcagt	gatgggttag	tggatggaag	3120
gggctgacag	acagccctcc	atctaaactg	ccccctctgc	cctgcgggtc	acaggaggga	3180
gggggaaggc	agggaggggc	tgggccccag	ttgtatttat	ttagtattta	ttcactttta	3240
tttagcacca	gggaagggga	caaggactag	ggtcctgggg	aacctgaccc	ctgacccctc	3300
atagccctca	ccctggggct	aggaaaatcca	gggtgggtgg	gatagggtata	agtgggtgtg	3360

```

gtatgcgtgt gtgtgtgtgt gtgaaaatgt gtgtgtgtgt atgtatgagg tacaacctgt 3420
tctgctttcc tcttcctgaa ttttattttt tgggaaaaga aaagtcaagg gtaggggtggg 3480
ccttcaggga gtgagggatt atcttttttt ttttttcttt ctttctttct tttttttttt 3540
tgagacagaa tctcgtctctg tcgcccaggc tggagtgcga tggcaccaatc tcggctcact 3600
gcatcctccg cctcccgggt tcaagtgatt ctcatgcctc agcctcctga gtagctggga 3660
ttacaggtc ctgccaccac gcccagctaa tttttgtttt gttttgtttg gagacagagt 3720
ctcgtattg tcaccagggc tggaatgatt tcagctcact gcaaccttcg ccacctgggt 3780
tccagcaatt ctcctgcctc agcctcccga gtagctgaga ttataggcac ctaccaccac 3840
gcccggctaa tttttgtatt tttagtagag acgggggtttc accatgttgg ccaggctgggt 3900
ctcgaactcc tgaccttagg tgatccactc gccttcactc cccaaagtgc tgggattaca 3960
ggcgtgagcc accgtgcctg gccacgcccc actaatTTTT gtatttttag tagagacagg 4020
gtttcaccat gttggccagg ctgctcttga actcctgacc tcaggtaatc gacctgcctc 4080
ggcctcccaa agtgctggga ttacaggtgt gagccaccac gcccggtaca tattttttaa 4140
attgaattct actatttatg tgatcctttt ggagtcagac agatgtgggt gcatcctaac 4200
tccatgtctc tgagcattag atttctcatt tgccaataat aatacctccc ttagaagttt 4260
gttgtgagga ttaaataatg taaataaaga actagcataa cgb 4303

```

<210> 12
 <211> 840
 <212> PRT
 <213> Homo sapien

<400> 12

```

Met Ser Gln Thr Gly Ser His Pro Gly Arg Gly Leu Ala Gly Arg Trp
 1          5          10          15
Leu Trp Gly Ala Gln Pro Cys Leu Leu Leu Pro Ile Val Pro Leu Ser
          20          25          30
Trp Leu Val Trp Leu Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
          35          40          45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
          50          55          60
Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
          65          70          75          80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
          85          90          95
Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
          100          105          110
Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
          115          120          125
Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
          130          135          140
Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
          145          150          155          160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
          165          170          175
Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
          180          185          190
Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
          195          200          205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
          210          215          220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
          225          230          235          240
Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
          245          250          255

```

Ser Ile Arg Asn Pro Val Ser Leu Val Val Thr Arg Leu Val Ile Leu
 260 265 270
 Gly Ser Gly Glu Glu Gly Pro Gln Val Gly Pro Ser Ala Ala Gln Thr
 275 280 285
 Leu Arg Ser Phe Cys Ala Trp Gln Arg Gly Leu Asn Thr Pro Glu Asp
 290 295 300
 Ser Asp Pro Asp His Phe Asp Thr Ala Ile Leu Phe Thr Arg Gln Asp
 305 310 315 320
 Leu Cys Gly Val Ser Thr Cys Asp Thr Leu Gly Met Ala Asp Val Gly
 325 330 335
 Thr Val Cys Asp Pro Ala Arg Ser Cys Ala Ile Val Glu Asp Asp Gly
 340 345 350
 Leu Gln Ser Ala Phe Thr Ala Ala His Glu Leu Gly His Val Phe Asn
 355 360 365
 Met Leu His Asp Asn Ser Lys Pro Cys Ile Ser Leu Asn Gly Pro Leu
 370 375 380
 Ser Thr Ser Arg His Val Met Ala Pro Val Met Ala His Val Asp Pro
 385 390 395 400
 Glu Glu Pro Trp Ser Pro Cys Ser Ala Arg Phe Ile Thr Asp Phe Leu
 405 410 415
 Asp Asn Gly Tyr Gly His Cys Leu Leu Asp Lys Pro Glu Ala Pro Leu
 420 425 430
 His Leu Pro Val Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln
 435 440 445
 Cys Gln Leu Thr Phe Gly Pro Asp Ser Arg His Cys Pro Gln Leu Pro
 450 455 460
 Pro Pro Cys Ala Ala Leu Trp Cys Ser Gly His Leu Asn Gly His Ala
 465 470 475 480
 Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
 485 490 495
 Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
 500 505 510
 Gln Asp Phe Asn Ile Pro Gln Ala Gly Gly Trp Gly Pro Trp Gly Pro
 515 520 525
 Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser
 530 535 540
 Arg Asp Cys Thr Arg Pro Val Pro Arg Asn Gly Gly Lys Tyr Cys Glu
 545 550 555 560
 Gly Arg Arg Thr Arg Phe Arg Ser Cys Asn Thr Glu Asp Cys Pro Thr
 565 570 575
 Gly Ser Ala Leu Thr Phe Arg Glu Glu Gln Cys Ala Ala Tyr Asn His
 580 585 590
 Arg Thr Asp Leu Phe Lys Ser Phe Pro Gly Pro Met Asp Trp Val Pro
 595 600 605
 Arg Tyr Thr Gly Val Ala Pro Gln Asp Gln Cys Lys Leu Thr Cys Gln
 610 615 620
 Ala Arg Ala Leu Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp
 625 630 635 640
 Gly Thr Pro Cys Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg
 645 650 655
 Cys Ile His Ala Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Lys Phe
 660 665 670
 Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
 675 680 685
 Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

690	695	700
Ile Pro Ala Gly Ala Thr His Ile Leu Val Arg Gln Gln Gly Asn Pro		
705	710	715
Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr		720
	725	730
Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val		735
	740	745
Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser		750
	755	760
Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln		765
	770	775
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe		780
785	790	795
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp		800
	805	810
Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro		815
	820	825
Trp Ala Gly Arg Lys Phe Ile Gly		830
835	840	

<210> 13
 <211> 1518
 <212> DNA
 <213> Rattus norvegicus

<400> 13	
actcactata gggctcgagc ggccgcccgg gcaggtcaga ggctcactgg cagctctcta	60
gacctgcgac gctgcttcta ttccgggtat gtgaacgcgg agccagactc ctttgctgct	120
gtaagcctat gcgggggtct ccgcggagcc tttggctacc aagggtcgga gtatgtcatt	180
agccctctgc ccaacaccag cgcgcctgag gcgcagcgtc atagccaggg cgcacacctt	240
ctccagcgcc ggggtgctcc cgtagggcct tccggagacc ctacctctcg ctgcgggggtg	300
gcctcgggct ggaaccccgc catcctgagg gccttggacc cttataaacc acggcggacg	360
ggcgtgggcg aaagccacaa ccggcgcagg tctgggcgcg ccaagcgctt cgtgtctata	420
ccacggtacg tggagacact ggtggtggcg gacgagtc aa tgggtcaagtt tcacggcgcg	480
gatttggaac attatctgct gacgctgctg gccacggcgg cgcgactcta ccgccacccc	540
agcatcctca accctatcaa catcgttgtg gtcaaggtgt tactcttagg agatcgtgac	600
actgggccc aagtcacagg caacgcggcc ctgactctgc gcaacttctg tgcctggcag	660
aaaaagttga acaaagtgag cgacaagcac ccgagtagt gggacacagc catcctcttc	720
accagacagg acctatgcgg ggctaccacc tgtgacacct tgggcatggc tgatgtgggc	780
accatgtgtg atcccaagag aagctgctct gtcacgagg acgatgggct tccgtcggcc	840
ttcaccactg cccatgagct gggccatgtg ttcaacatgc cccatgacaa cgtgaagggtg	900
tgtgaggagg tgtttgggaa gctcagagcc aaccacatga tgtctccgac actcatccag	960
atcgaccgtg ccaaccctg gtcagcctgc agtgctgcca ttatcaccca cttcctggac	1020
agcgggcaag gtgactgcct cctggaccag ccagcaagc ccatcacctt gcctgaggac	1080
ctgccaggca caagctacag tttgagccaa cagtgcgagc tggccttttg ggtgggctct	1140
aagccctgcc catatatgca gtactgtaca aagctgtggt gcaccggcaa ggccaagggg	1200
cagatggtgt gccagactcg ccacttcccc tgggcagatg gcaccagctg tgggtgagggc	1260
aagttctgcc tcaagggagc ctgcgtggag agacacaacc caaacaagta ccgggtggac	1320
ggcccttggg ccaagtggga gccttatggt cctgtctcgc gcacctgcgg tgggggcgcg	1380
cagctggccc ggaagcaagt gcaagcaacc ctaccctgc caacgggcgg gaagtactgc	1440
gagggagtga gagtgaata ccgatcttgc aacttggagc cctgccccag ctcagcctct	1500
ggcaagagct tccgggaa	1518

<210> 14

<211> 505

<212> PRT

<213> Rattus norvegicus

<400> 14

```

Thr His Tyr Arg Ala Arg Ala Ala Ala Arg Ala Gly Gln Arg Leu Thr
 1          5          10          15
Gly Ser Ser Leu Asp Leu Arg Arg Cys Phe Tyr Ser Gly Tyr Val Asn
 20          25          30
Ala Glu Pro Asp Ser Phe Ala Ala Val Ser Leu Cys Gly Gly Leu Arg
 35          40          45
Gly Ala Phe Gly Tyr Gln Gly Ala Glu Tyr Val Ile Ser Pro Leu Pro
 50          55          60
Asn Thr Ser Ala Pro Glu Ala Gln Arg His Ser Gln Gly Ala His Leu
 65          70          75
Leu Gln Arg Arg Gly Ala Pro Val Gly Pro Ser Gly Asp Pro Thr Ser
 85          90          95
Arg Cys Gly Val Ala Ser Gly Trp Asn Pro Ala Ile Leu Arg Ala Leu
100          105          110
Asp Pro Tyr Lys Pro Arg Arg Thr Gly Val Gly Glu Ser His Asn Arg
115          120          125
Arg Arg Ser Gly Arg Ala Lys Arg Phe Val Ser Ile Pro Arg Tyr Val
130          135          140
Glu Thr Leu Val Val Ala Asp Glu Ser Met Val Lys Phe His Gly Ala
145          150          155
Asp Leu Glu His Tyr Leu Leu Thr Leu Leu Ala Thr Ala Ala Arg Leu
165          170          175
Tyr Arg His Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys
180          185          190
Val Leu Leu Leu Gly Asp Arg Asp Thr Gly Pro Lys Val Thr Gly Asn
195          200          205
Ala Ala Leu Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn
210          215          220
Lys Val Ser Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe
225          230          235
Thr Arg Gln Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met
245          250          255
Ala Asp Val Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile
260          265          270
Glu Asp Asp Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly
275          280          285
His Val Phe Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val
290          295          300
Phe Gly Lys Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln
305          310          315
Ile Asp Arg Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr
325          330          335
Asp Phe Leu Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser
340          345          350
Lys Pro Ile Thr Leu Pro Glu Asp Leu Pro Gly Thr Ser Tyr Ser Leu
355          360          365
Ser Gln Gln Cys Glu Leu Ala Phe Gly Val Gly Ser Lys Pro Cys Pro
370          375          380
Tyr Met Gln Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly
385          390          395          400

```

Gln Met Val Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser
 405 410 415
 Cys Gly Glu Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Arg His
 420 425 430
 Asn Pro Asn Lys Tyr Arg Val Asp Gly Pro Trp Ala Lys Trp Glu Pro
 435 440 445
 Tyr Gly Pro Cys Ser Arg Thr Cys Gly Gly Gly Ala Gln Leu Ala Arg
 450 455 460
 Arg Gln Val Gln Ala Thr Leu Pro Leu Pro Thr Gly Gly Lys Tyr Cys
 465 470 475 480
 Glu Gly Val Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro
 485 490 495
 Ser Ser Ala Ser Gly Lys Ser Phe Arg
 500 505

<210> 15

<211> 1455

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1455)

<223> n = A,T,C or G

<400> 15

gatgcatcta	agccctgggc	caaatgcact	tcagccacca	tcacagaatt	cctggatgat	60
ggccatggta	actgtttgct	ggacctaacc	cgaaagcaga	tcctggggccc	cgaagaactc	120
ccaggacaga	cctacgatgc	cacccagcag	tgcaacctta	cattcggggcc	tgagtactcc	180
gtgtgtcccg	gcattggatg	ctgtgctccc	ctgtgggtgtg	ctgtgggtacg	ccaggggccag	240
atgggtctgtc	tgaccaagaa	gcttcctgcg	gtgggaaggga	cgccttggtg	aaagggggaga	300
atctgcctgc	agggcaaatg	tgtggacaaa	accaagaaaa	aatattattc	aacgtcaagc	360
catggcaact	ggggatcttg	gggatcctgg	ggccagtgtt	ctcgtcatg	tggaggagga	420
gtgcagtttg	cctatcgctg	ctgtaataac	cctgctccca	gaaacaacgg	acgctactgc	480
acaggggaaga	gggccatcta	ccgctcctgc	agtctcatgc	cctgcccacc	caatggtaaa	540
tcatttcgtc	atgaacagtg	tgaggccaaa	aatggctatc	agtctgatgc	aaaaggagtc	600
aaaacttttg	tggaaatggg	tcccaaatat	gcaagtgtcc	tgcccagcga	tgtgtgcaag	660
ctgacctgca	gagccaaagg	gactgggtac	tatgtggtat	tttctccaaa	ggtgaccgat	720
ggcactgaat	gtaggccgta	cagtaattcc	gtctgcgtcc	gggggaagtg	tgtgagaact	780
ggctgtgacg	gcatcattgg	ctcaaagctg	cagtatgaca	agtgcggagt	atgtggagga	840
gacaactcca	gctgtacaaa	gattgttgga	acctttaata	agaaaagtaa	gggttcanc	900
gacgtgggtga	ggattcctga	aggggcaacc	cacataaaa	ttcgacagtt	caaagccaaa	960
gaccagacta	gattcactgc	ctatttagcc	ctgaaaaaga	aaaacgggtg	gtaccttatt	1020
aatggaaagt	acatgatctc	cacttcagag	actatcattg	acatcaatgg	aacagtcatt	1080
aactatagcg	gttggagcca	cagggatgac	ttcctgcatg	gcatgggcta	ctctgccacg	1140
aaggaaattc	taatagtgc	gattcttgca	acagacccca	ctaaaccatt	agatgtccgt	1200
tatagctttt	ttgttcccaa	gaagtccact	ccaaaagtaa	actctgtcac	tagtcatggc	1260
agcaataaag	tgggatcaca	cacttcgcag	ccgcagtggg	tcacggggccc	atggctcgcc	1320
tgctctagga	cctgtgacac	aggttgacac	accagaacgg	tgcatgcca	ggatggaaac	1380
cggaagttag	caaaaggatg	tcctctctcc	caaaggcctt	ctgcgtttaa	gcaatgcttg	1440
ttgaagaaat	gttag					1455

<210> 16

<211> 484

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(484)

<223> Xaa = Any Amino Acid

<400> 16

```

Asp Ala Ser Lys Pro Trp Ser Lys Cys Thr Ser Ala Thr Ile Thr Glu
 1          5          10          15
Phe Leu Asp Asp Gly His Gly Asn Cys Leu Leu Asp Leu Pro Arg Lys
 20          25          30
Gln Ile Leu Gly Pro Glu Glu Leu Pro Gly Gln Thr Tyr Asp Ala Thr
 35          40          45
Gln Gln Cys Asn Leu Thr Phe Gly Pro Glu Tyr Ser Val Cys Pro Gly
 50          55          60
Met Asp Val Cys Ala Pro Leu Trp Cys Ala Val Val Arg Gln Gly Gln
 65          70          75          80
Met Val Cys Leu Thr Lys Lys Leu Pro Ala Val Glu Gly Thr Pro Cys
 85          90          95
Gly Lys Gly Arg Ile Cys Leu Gln Gly Lys Cys Val Asp Lys Thr Lys
100          105          110
Lys Lys Tyr Tyr Ser Thr Ser Ser His Gly Asn Trp Gly Ser Trp Gly
115          120          125
Ser Trp Gly Gln Cys Ser Arg Ser Cys Gly Gly Gly Val Gln Phe Ala
130          135          140
Tyr Arg Arg Cys Asn Asn Pro Ala Pro Arg Asn Asn Gly Arg Tyr Cys
145          150          155          160
Thr Gly Lys Arg Ala Ile Tyr Arg Ser Cys Ser Leu Met Pro Cys Pro
165          170          175
Pro Asn Gly Lys Ser Phe Arg His Glu Gln Cys Glu Ala Lys Asn Gly
180          185          190
Tyr Gln Ser Asp Ala Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro
195          200          205
Lys Tyr Ala Ser Val Leu Pro Ser Asp Val Cys Lys Leu Thr Cys Arg
210          215          220
Ala Lys Gly Thr Gly Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp
225          230          235          240
Gly Thr Glu Cys Arg Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys
245          250          255
Cys Val Arg Thr Gly Cys Asp Gly Ile Ile Gly Ser Lys Leu Gln Tyr
260          265          270
Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Ile
275          280          285
Val Gly Thr Phe Asn Lys Lys Ser Lys Gly Ser Xaa Asp Val Val Arg
290          295          300
Ile Pro Glu Gly Ala Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys
305          310          315          320
Asp Gln Thr Arg Phe Thr Ala Tyr Leu Ala Leu Lys Lys Lys Asn Gly
325          330          335
Glu Tyr Leu Ile Asn Gly Lys Tyr Met Ile Ser Thr Ser Glu Thr Ile
340          345          350
Ile Asp Ile Asn Gly Thr Val Met Asn Tyr Ser Gly Trp Ser His Arg
355          360          365

```

Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
 370 375 380
 Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
 385 390 395 400
 Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn Ser Val
 405 410 415
 Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln Pro Gln
 420 425 430
 Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp Thr Gly
 435 440 445
 Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys Leu Ala
 450 455 460
 Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln Cys Leu
 465 470 475 480
 Leu Lys Lys Cys

<210> 17
 <211> 423
 <212> DNA
 <213> Bos taurus

<400> 17
 tttaggagg agcagtggtga ggccaaaaat ggatatcagt ctgatgcaaa aggagtcaaa 60
 acgtttgtgg aatgggttcc caaatatgct ggtgtcctgc ccggagacgt gtgcaaaactg 120
 acctgcagag ctaagggcac tggctactac gtggtgttct ctccaaagggt gaccgatggg 180
 acagagtgcg ggccatacag caattccgtg tgtgtccggg ggaagtgtgt gcggacaggc 240
 tgtgacagca tcattggctc gaagctgcag tatgacaaat gtggcgtctg tggaggagac 300
 aactccagtt gcacaaagggt ggtcgggaacc ttcaataaaa aaagtaagggt ttacactgac 360
 gtogtgagga tccccgaagg ggcgactcac ataaaagtcc gacagttcaa agccaaagac 420
 cag 423

<210> 18
 <211> 141
 <212> PRT
 <213> Bos taurus

<400> 18
 Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
 1 5 10 15
 Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
 20 25 30
 Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
 35 40 45
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 50 55 60
 Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly
 65 70 75 80
 Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
 85 90 95
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn
 100 105 110
 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 115 120 125
 Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln

130

135

140

<210> 19
 <211> 637
 <212> DNA
 <213> Bos taurus

<400> 19

```

ggaaaccctg gccatttga gcaactacct ggccctgaag ctccccgatg gtcctatgc      60
cctcaacggt gaatacacgc tgatcccgtc cccacacagac gtggtactgc ccggggccgt      120
cagcctgctg tacagcgggg ccaactgcagc ctccggagaca ctgtcaggac acggggcccct      180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg cccgcctcag      240
atacagcttt ttcgtgccgc gaccgcgacc ggtcccctcc acgccacgcc ccaactccca      300
ggactggctg cgccgcaagt cacagattct ggagatcctc cggcgccgct cctggggccg      360
caggaaataa cctcaccatc ccggctgccc ttcttgggca ccggggcctc ggacttagct      420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag      480
tgagccccgc ctctcctccc cgcgctaccg agcaggctgg ccctgccggg gtttcctgcc      540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct      600
gcctgctgg tcacaggagg gagggggaag gcaggga      637
  
```

<210> 20
 <211> 122
 <212> PRT
 <213> Bos taurus

<400> 20

```

Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
 1           5           10           15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
 20           25           30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
 35           40           45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
 50           55           60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
 65           70           75           80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
 85           90           95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
 100          105          110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
 115          120
  
```

<210> 21
 <211> 1143
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(1143)
 <223> n = A,T,C or G

<400> 21

```

actcactata gggctcgtgc ggccgcccgg gcaggcatct ttaagcatcc cagcatcctc      60
  
```

```

aaccccatca acatcgttgt ggtcaagggt ctgcttctta gagatcgtga ctccggggccc 120
aaggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg 180
aacaagtga gtgacaagca ccccgagtag tgggacactg ccacccctct caccaggcag 240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt 300
gacccaaga gaagctgtct tgtcattgag gacgatgggc ttccatcagc cttcaccact 360
gcccacggagc tggggcacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag 420
gtgtttggga agctccgagc caaccacatg atgtccccga ccctcatcca gatcgaccgt 480
gccaacccct ggtcagcctg cagtgtgtgc atcatcaccg actttctgga cagcggggcac 540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc 600
gccagctaca ccctgagcca gcartgcgag ctggcttttg gcgtgggctt caagccctgt 660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatgggtg 720
tgccaaaccc gccacttccc ctgggcccgt ggcaccagtt gtggcgaggg caagttctgc 780
ctcaaagggg cctgcgtgga aaracacaac ctcaacaagc acagggtgga tgggtcctgg 840
gccaatggg atccctatgg cccctgctcg cgcacatgtg gtgggggctg gcagctggcc 900
aggaggcagn tgcaccaacc ccnccctg ccaacngggg gcaagtactg cgagggagtg 960
agggtgaaat accgatcctg caacctggag ccctgccccg gctcagcctc cggaaagagc 1020
ttccggggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact 1080
ctgcgcgtgg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc 1140
atc 1143

```

<210> 22

<211> 381

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(381)

<223> Xaa = Any Amino Acid

<400> 22

```

Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Ile Phe Lys His
1          5          10          15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys Val Leu Leu
20          25          30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
35          40          45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
50          55          60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65          70          75          80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
85          90          95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
100         105         110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
115         120         125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
130         135         140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145         150         155         160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
165         170         175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
180         185         190

```

Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
 195 200 205
 Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
 210 215 220
 Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
 225 230 235 240
 Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
 245 250 255
 Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
 260 265 270
 Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
 275 280 285
 Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
 290 295 300
 His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
 305 310 315 320
 Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
 325 330 335
 Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
 340 345 350
 Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
 355 360 365
 Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
 370 375 380

<210> 23

<211> 297

<212> DNA

<213> Rattus norvegicus

<400> 23

tccgcccttc	cgggaggaac	agtgtagaaa	atataatgcc	tacaaccaca	cggacctgga	60
tgggaatttc	cttcagtggg	tcccaata	ctcaggagtg	tcccccgag	accgatgcaa	120
actgttttgc	agagcccgtg	ggaggagtga	gttcaaagtg	tttgaaacta	aggtgatcga	180
tggcactctg	tgcggaccgg	atactctggc	catctgtgtg	cggggacagt	gcgttaaggc	240
tggctgtgac	catgtggtga	actcacctaa	gaagctggac	aagtgcggta	tctgtgg	297

<210> 24

<211> 98

<212> PRT

<213> Rattus norvegicus

<400> 24

Pro	Pro	Phe	Arg	Glu	Glu	Gln	Cys	Glu	Lys	Tyr	Asn	Ala	Tyr	Asn	His
1				5					10					15	
Thr	Asp	Leu	Asp	Gly	Asn	Phe	Leu	Gln	Trp	Val	Pro	Lys	Tyr	Ser	Gly
		20						25						30	
Val	Ser	Pro	Arg	Asp	Arg	Cys	Lys	Leu	Phe	Cys	Arg	Ala	Arg	Gly	Arg
		35					40					45			
Ser	Glu	Phe	Lys	Val	Phe	Glu	Thr	Lys	Val	Ile	Asp	Gly	Thr	Leu	Cys
	50					55					60				
Gly	Pro	Asp	Thr	Leu	Ala	Ile	Cys	Val	Arg	Gly	Gln	Cys	Val	Lys	Ala
	65				70				75					80	
Gly	Cys	Asp	His	Val	Val	Asn	Ser	Pro	Lys	Lys	Leu	Asp	Lys	Cys	Gly
				85					90					95	

Ile Cys

<210> 25
 <211> 823
 <212> DNA
 <213> Rattus norvegicus

<400> 25
 cccctggatg tgggtcaaagt gcagtcggaa gtacatcacc gagttcttag acactgggta 60
 tggagagtgc ttgttaaagt aacctcaatc caggacctat cctttgcctt cccaactgcc 120
 cggcctttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
 gtgccccatat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
 aggctgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
 ctgcaagttt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
 gggaagtgtg agtcactttg gggcctgctc aagaacatgt ggaggaggca tcagaacagc 420
 catcagagag tgcaacagac cagagccaaa aaatggtggg aggtactgtg tagggaggag 480
 aatraagtgc aaatcctgca acaccgagcc ctgcccgaa cacaagcgag acttccgtga 540
 ggagcagtgt gcttactttg acggcaagca tttcaacatc aatggtctgc tgcccagtgt 600
 acgctgggtc cctaagtaca gtggaatttt gatgaaggac cgatgcaagt tgttctgcag 660
 agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaacccccctg 720
 tggccaggac acaaatgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
 tactttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
 <211> 274
 <212> PRT
 <213> Rattus norvegicus

<220>
 <221> VARIANT
 <222> (1)...(274)
 <223> Xaa = Any Amino Acid

<400> 26
 Pro Trp Met Trp Ser Lys Cys Ser Arg Lys Tyr Ile Thr Glu Phe Leu
 1 5 10 15
 Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
 20 25 30
 Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
 35 40 45
 Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
 50 55 60
 Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
 65 70 75 80
 Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
 85 90 95
 Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
 100 105 110
 Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
 115 120 125
 Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
 130 135 140
 Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
 145 150 155 160

[illegible]

```
<210> 27
<211> 1073
<212> PRT
<213> Homo sapien
```

	<400> 27														
Met 1	Gln	Phe	Val	Ser 5	Trp	Ala	Thr	Leu 10	Leu	Thr	Leu	Leu	Val	Arg 15	Asp
Leu	Ala	Glu	Met 20	Gly	Ser	Pro	Asp 25	Ala	Ala	Ala	Val	Arg 30	Lys	Asp	
Arg	Leu	His 35	Pro	Arg	Gln	Val	Lys 40	Leu	Leu	Glu	Thr	Leu 45	Gly	Glu	Tyr
Glu	Ile	Val	Ser	Pro	Ile	Arg	Val 55	Asn	Ala	Leu	Gly 60	Glu	Pro	Phe	Pro
Thr 65	Asn	Val	His	Phe	Lys	Arg	Thr 70	Arg	Arg	Ser 75	Ile	Asn	Ser	Ala	Thr 80
Asp	Pro	Trp	Pro	Ala 85	Phe	Ala	Ser	Ser 90	Ser	Ser	Ser	Ser	Thr	Ser	Ser
Gln	Ala	His	Tyr 100	Arg	Leu	Ser	Ala 105	Phe	Gly	Gln	Gln	Phe	Leu 110	Phe	Asn
Leu	Thr	Ala	Asn 115	Ala	Gly	Phe	Ile 120	Ala	Pro	Leu	Phe	Thr 125	Val	Thr	Leu
Leu	Gly	Thr	Pro	Gly	Val	Asn	Gln 135	Thr	Lys	Phe	Tyr 140	Ser	Glu	Glu	Glu
Ala 145	Glu	Leu	Lys	His	Cys	Phe	Tyr 150	Lys	Gly	Tyr 155	Val	Asn	Thr	Asn	Ser 160
Glu	His	Thr	Ala	Val 165	Ile	Ser	Leu	Cys	Ser 170	Gly	Met	Leu	Gly	Thr	Phe
Arg	Ser	His	Asp	Gly 180	Asp	Tyr	Phe 185	Ile	Glu	Pro	Leu	Gln	Ser	Met	Asp
Glu	Gln	Glu	Asp	Glu	Glu	Glu	Gln 200	Asn	Lys	Pro	His	Ile 205	Ile	Tyr	Arg
Arg	Ser	Ala	Pro	Gln	Arg	Glu	Pro 215	Ser	Thr	Gly	Arg	His	Ala	Cys	Asp
Thr 225	Ser	Glu	His	Lys	Asn	Arg	His 230	Ser	Lys	Asp 235	Lys	Lys	Lys	Thr	Arg
Ala	Arg	Lys	Trp	Gly 245	Glu	Arg	Ile	Asn	Leu	Ala	Gly	Asp	Val	Ala	Ala
Leu	Asn	Ser	Gly	Leu	Ala	Thr	Glu	Ala	Phe	Ser	Ala	Tyr	Gly	Asn	Lys

			260					265					270		
Thr	Asp	Asn	Thr	Arg	Glu	Lys	Arg	Thr	His	Arg	Arg	Thr	Lys	Arg	Phe
		275					280					285			
Leu	Ser	Tyr	Pro	Arg	Phe	Val	Glu	Val	Leu	Val	Val	Ala	Asp	Asn	Arg
		290					295				300				
Met	Val	Ser	Tyr	His	Gly	Glu	Asn	Leu	Gln	His	Tyr	Ile	Leu	Thr	Leu
305					310					315					320
Met	Ser	Ile	Val	Ala	Ser	Ile	Tyr	Lys	Asp	Pro	Ser	Ile	Gly	Asn	Leu
				325					330					335	
Ile	Asn	Ile	Val	Ile	Val	Asn	Leu	Ile	Val	Ile	His	Asn	Glu	Gln	Asp
			340					345					350		
Gly	Pro	Ser	Ile	Ser	Phe	Asn	Ala	Gln	Thr	Thr	Leu	Lys	Asn	Leu	Cys
		355					360					365			
Gln	Trp	Gln	His	Ser	Lys	Asn	Ser	Pro	Gly	Gly	Ile	His	His	Asp	Thr
		370				375					380				
Ala	Val	Leu	Leu	Thr	Arg	Gln	Asp	Ile	Cys	Arg	Ala	His	Asp	Lys	Cys
385					390					395				400	
Asp	Thr	Leu	Gly	Leu	Ala	Glu	Leu	Gly	Thr	Ile	Cys	Asp	Pro	Tyr	Arg
			405					410						415	
Ser	Cys	Ser	Ile	Ser	Glu	Asp	Ser	Gly	Leu	Ser	Thr	Ala	Phe	Thr	Ile
			420					425					430		
Ala	His	Glu	Leu	Gly	His	Val	Phe	Asn	Met	Pro	His	Asp	Asp	Asn	Asn
		435					440					445			
Lys	Cys	Lys	Glu	Glu	Gly	Val	Lys	Ser	Pro	Gln	His	Val	Met	Ala	Pro
		450				455					460				
Thr	Leu	Asn	Phe	Tyr	Thr	Asn	Pro	Trp	Met	Trp	Ser	Lys	Cys	Ser	Arg
465					470					475				480	
Lys	Tyr	Ile	Thr	Glu	Phe	Leu	Asp	Thr	Gly	Tyr	Gly	Glu	Cys	Leu	Leu
			485					490						495	
Asn	Glu	Pro	Glu	Ser	Arg	Pro	Tyr	Pro	Leu	Pro	Val	Gln	Leu	Pro	Gly
			500					505					510		
Ile	Leu	Tyr	Asn	Val	Asn	Lys	Gln	Cys	Glu	Leu	Ile	Phe	Gly	Pro	Gly
		515					520					525			
Ser	Gln	Val	Cys	Pro	Tyr	Met	Met	Gln	Cys	Arg	Arg	Leu	Trp	Cys	Asn
		530				535					540				
Asn	Val	Asn	Gly	Val	His	Lys	Gly	Cys	Arg	Thr	Gln	His	Thr	Pro	Trp
545					550					555				560	
Ala	Asp	Gly	Thr	Glu	Cys	Glu	Pro	Gly	Lys	His	Cys	Lys	Tyr	Gly	Phe
			565					570						575	
Cys	Val	Pro	Lys	Glu	Met	Asp	Val	Pro	Val	Thr	Asp	Gly	Ser	Trp	Gly
			580					585					590		
Ser	Trp	Ser	Pro	Phe	Gly	Thr	Cys	Ser	Arg	Thr	Cys	Gly	Gly	Gly	Ile
		595					600					605			
Lys	Thr	Ala	Ile	Arg	Glu	Cys	Asn	Arg	Pro	Glu	Pro	Lys	Asn	Gly	

Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 705 710 715 720
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 725 730 735
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 740 745 750
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
 755 760 765
 Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
 770 775 780
 Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
 785 790 795 800
 Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
 805 810 815
 Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
 820 825 830
 Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
 835 840 845
 Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
 850 855 860
 Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
 865 870 875 880
 Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
 885 890 895
 Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
 900 905 910
 Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
 915 920 925
 Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
 930 935 940
 Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
 945 950 955 960
 Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
 965 970 975
 Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
 980 985 990
 Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
 995 1000 1005
 Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
 1010 1015 1020
 Cys Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His
 1025 1030 1035 1040
 Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
 1045 1050 1055
 Trp Lys Ser Gly Asp Trp Ser Glu Val Arg Trp Glu Gly Cys Tyr Phe
 1060 1065 1070
 Pro

<210> 28
 <211> 951
 <212> PRT
 <213> Mus musculus

<400> 28
 Met Gly Asp Val Gln Arg Ala Ala Arg Ser Arg Gly Ser Leu Ser Ala

1	5	10	15
His Met Leu Leu Leu Leu Leu Ala Ser Ile Thr Met Leu Leu Cys Ala			
	20	25	30
Arg Gly Ala His Gly Arg Pro Thr Glu Glu Asp Glu Glu Leu Val Leu			
	35	40	45
Pro Ser Leu Glu Arg Ala Pro Gly His Asp Ser Thr Thr Thr Arg Leu			
	50	55	60
Arg Leu Asp Ala Phe Gly Gln Gln Leu His Leu Lys Leu Gln Pro Asp			
65	70	75	80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser			
	85	90	95
Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His			
	100	105	110
Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala			
	115	120	125
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu			
	130	135	140
Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala			
145	150	155	160
Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile			
	165	170	175
Leu Arg Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met			
	180	185	190
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn			
	195	200	205
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly			
	210	215	220
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser			
225	230	235	240
Pro Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Asp			
	245	250	255
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val			
	260	265	270
Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu			
	275	280	285
Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu			
	290	295	300
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln			
305	310	315	320
Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr			
	325	330	335
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp			
	340	345	350
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser			
	355	360	365
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala			
	370	375	380
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His			
385	390	395	400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser			
	405	410	415
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala			
	420	425	430
Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met			
	435	440	445

Asp Lys Pro Gln Asn Pro Ile Lys Leu Pro Ser Asp Leu Pro Gly Thr
 450 455 460
 Leu Tyr Asp Ala Asn Arg Gln Cys Gln Phe Thr Phe Gly Glu Glu Ser
 465 470 475 480
 Lys His Cys Pro Asp Ala Ala Ser Thr Cys Thr Thr Leu Trp Cys Thr
 485 490 495
 Gly Thr Ser Gly Gly Leu Leu Val Cys Gln Thr Lys His Phe Pro Trp
 500 505 510
 Ala Asp Gly Thr Ser Cys Gly Glu Gly Lys Trp Cys Val Ser Gly Lys
 515 520 525
 Cys Val Asn Lys Thr Asp Met Lys His Phe Ala Thr Pro Val His Gly
 530 535 540
 Ser Trp Gly Pro Trp Gly Pro Trp Gly Asp Cys Ser Arg Thr Cys Gly
 545 550 555 560
 Gly Gly Val Gln Tyr Thr Met Arg Glu Cys Asp Asn Pro Val Pro Lys
 565 570 575
 Asn Gly Gly Lys Tyr Cys Glu Gly Lys Arg Val Arg Tyr Arg Ser Cys
 580 585 590
 Asn Ile Glu Asp Cys Pro Asp Asn Asn Gly Lys Thr Phe Arg Glu Glu
 595 600 605
 Gln Cys Glu Ala His Asn Glu Phe Ser Lys Ala Ser Phe Gly Asn Glu
 610 615 620
 Pro Thr Val Glu Trp Thr Pro Lys Tyr Ala Gly Val Ser Pro Lys Asp
 625 630 635 640
 Arg Cys Lys Leu Thr Cys Glu Ala Lys Gly Ile Gly Tyr Phe Phe Val
 645 650 655
 Leu Gln Pro Lys Val Val Asp Gly Thr Pro Cys Ser Pro Asp Ser Thr
 660 665 670
 Ser Val Cys Val Gln Gly Gln Cys Val Lys Ala Gly Cys Asp Arg Ile
 675 680 685
 Ile Asp Ser Lys Lys Lys Phe Asp Lys Cys Gly Val Cys Gly Gly Asn
 690 695 700
 Gly Ser Thr Cys Lys Lys Met Ser Gly Ile Val Thr Ser Thr Arg Pro
 705 710 715 720
 Gly Tyr His Asp Ile Val Thr Ile Pro Ala Gly Ala Thr Asn Ile Glu
 725 730 735
 Val Lys His Arg Asn Gln Arg Gly Ser Arg Asn Asn Gly Ser Phe Leu
 740 745 750
 Ala Ile Arg Ala Ala Asp Gly Thr Tyr Ile Leu Asn Gly Asn Phe Thr
 755 760 765
 Leu Ser Thr Leu Glu Gln Asp Leu Thr Tyr Lys Gly Thr Val Leu Arg
 770 775 780
 Tyr Ser Gly Ser Ser Ala Ala Leu Glu Arg Ile Arg Ser Phe Ser Pro
 785 790 795 800
 Leu Lys Glu Pro Leu Thr Ile Gln Val Leu Met Val Gly His Ala Leu
 805 810 815
 Arg Pro Lys Ile Lys Phe Thr Tyr Phe Met Lys Lys Lys Thr Glu Ser
 820 825 830
 Phe Asn Ala Ile Pro Thr Phe Ser Glu Trp Val Ile Glu Glu Trp Gly
 835 840 845
 Glu Cys Ser Lys Thr Cys Gly Ser Gly Trp Gln Arg Arg Val Val Gln
 850 855 860
 Cys Arg Asp Ile Asn Gly His Pro Ala Ser Glu Cys Ala Lys Glu Val
 865 870 875 880
 Lys Pro Ala Ser Thr Arg Pro Cys Ala Asp Leu Pro Cys Pro His Trp

<210> 32
 <211> 6
 <212> PRT
 <213> Unknown

<220>
 <223> Semiconserved sequence of ADAMTS protein domain
 that binds to the extracellular matrix

<400> 32
 Phe Arg Glu Glu Gln Cys
 1 5

<210> 33
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide derived from analysis of the
 sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
 <222> (1)...(18)
 <223> n = A,T,C or G

<400> 33
 ttymgngarg arcartgy

18

<210> 34
 <211> 18
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Oligonucleotide derived from analysis of the
 sequences from ADAMTS-1 (mouse) and ADAMTS-3 (rat)

<221> misc_feature
 <222> (1)...(18)
 <223> n = A,T,C or G

<400> 34
 rcanayncr cayttrtc

18

<210> 35
 <211> 4
 <212> PRT
 <213> Homo sapien

<220>
 <223> Consensus catalytic sequence site based on ADAM
 and snake venom metalloproteases

<221> VARIANT
<222> (3) ... (3)
<223> Xaa = Lysine or Arginine

<221> VARIANT
<222> (1) ... (4)
<223> Xaa = Any Amino Acid

<400> 35
Arg Xaa Xaa Arg
1

<210> 36
<211> 7
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<221> VARIANT
<222> (2) ... (2)
<223> Xaa = Serine or Glycine

<221> VARIANT
<222> (1) ... (7)
<223> Xaa = Any Amino Acid

<400> 36
Trp Xaa Xaa Trp Ser Xaa Trp
1 5

<210> 37
<211> 6
<212> PRT
<213> Unknown

<220>
<223> Conserved heparin binding segment of internal TSP1
motif of ADAM-TS family members

<400> 37
Cys Ser Val Thr Cys Gly
1 5

<210> 38
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 38

caggggaaac agacgatgac aact

24

<210> 39
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 39
tgcggttaacc caagccacac t

21

<210> 40
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 40
gtgcgctggg tccctaaata c

21

<210> 41
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer

<400> 41
aaaatcacag gttggcagcg g

21

<210> 42
<211> 12
<212> PRT
<213> Unknown

<220>
<223> Zn binding site

<400> 42
His Glu Leu Gly His Asn Leu Gly Ile Arg His Asp
1 5 10

<210> 43
<211> 12
<212> PRT
<213> Unknown

<220>
<223> Zn binding site

<400> 43

His Glu Leu Gly His Asn Phe Gly Ala Glu His Asp
1 5 10

<210> 44

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Zn binding site

<400> 44

His Glu Ile Gly His Asn Phe Gly Ser Pro His Asp
1 5 10

<210> 45

<211> 12

<212> PRT

<213> Homo sapien

<400> 45

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 46

<211> 12

<212> PRT

<213> Homo sapien

<400> 46

His Glu Thr Gly His Val Leu Gly Met Glu His Asp
1 5 10

<210> 47

<211> 12

<212> PRT

<213> Homo sapien

<400> 47

His Glu Leu Gly His Val Phe Asn Met Leu His Asp
1 5 10

<210> 48

<211> 12

<212> PRT

<213> Homo sapien

<400> 48

His Glu Ile Gly His Leu Leu Gly Leu Ser His Asp
1 5 10

<210> 49

<211> 12

<212> PRT

<213> Homo sapien

<400> 49

His Glu Leu Gly His Val Phe Asn Met Pro His Asp
1 5 10

<210> 50

<211> 12

<212> PRT

<213> C. elegans

<400> 50

His Glu Leu Gly His Val Phe Ser Ile Pro His Asp
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Unknown

<220>

<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT

<222> (1)...(12)

<223> Xaa = Any Amino Acid

<400> 51

His Glu Xaa Gly His Xaa Xaa Gly Xaa Xaa His Asp
1 5 10

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



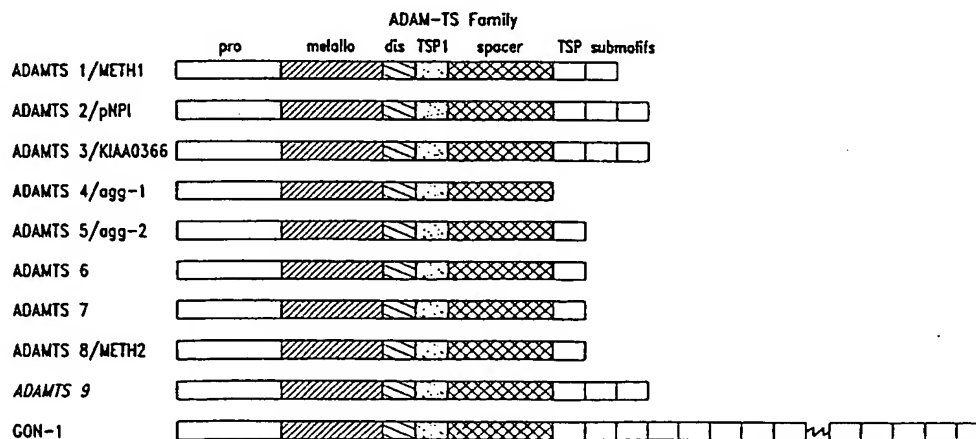
(43) International Publication Date
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number
WO 00/53774 A3

- (51) International Patent Classification⁷: C12N 15/57, 15/63, 9/64, A61K 38/48, C07K 16/40, C12Q 1/37
- (21) International Application Number: PCT/US00/06237
- (22) International Filing Date: 8 March 2000 (08.03.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/264,585 8 March 1999 (08.03.1999) US
- (71) Applicant (for all designated States except US): NEUROCRINE BIOSCIENCES, INC. [US/US]; 10555 Science Center Drive, San Diego, CA 92121 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KELNER, Gregory, S. [US/US]; 725 Muirlands Vista Way, La Jolla, CA 92037 (US). CLARK, Melody [US/US]; 7075 Charmant Drive #20, San Diego, CA 92122 (US). MAKI, Richard, A. [US/US]; 4175-174 Porte de Palmas, San Diego, CA 92122 (US).
- (74) Agents: CHRISTIANSEN, William, T. et al.; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).
- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
18 January 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METALLOPROTEINASES AND METHODS OF USE THEREFOR



(57) Abstract: Members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

WO 00/53774 A3

INTERNATIONAL SEARCH REPORT

International Application No.

I /US 00/06237

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/57 C12N15/63 C12N9/64 A61K38/48 C07K16/40 C12Q1/37		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N A61K C07K C12Q		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 55643 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 10 December 1998 (1998-12-10) & EP 1 004 674 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 31 May 2000 (2000-05-31) --- -/--	1,3-11, 17-21, 28,29, 31,32
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
29 June 2000		1 3. 10. 00
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016		Authorized officer MONTERO LOPEZ B.

INTERNATIONAL SEARCH REPORT

International Application No

F../US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KOUJI KUNO ET AL.: "Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 1, 3 January 1997 (1997-01-03), pages 556-562, XP002076038</p> <p>MD US</p> <p>cited in the application</p> <p>abstract</p> <p>page 558, left-hand column, paragraph 2</p> <p>-page 559, left-hand column, paragraph 2; figure 2</p> <p>page 559, left-hand column, paragraph 4</p> <p>page 561, right-hand column, last paragraph -page 562, left-hand column, paragraph 1</p>	<p>1,3-11, 17,20, 21,28, 29,31,32</p>
X	<p>---</p> <p>KOUJI KUNO ET AL.: "The exon/intron organization and chromosomal mapping of the mouse ADAMTS-1 gene encoding an ADAM family protein with TPS motifs"</p> <p>GENOMICS, vol. 46, no. 3, 15 December 1997 (1997-12-15), pages 466-471, XP000922766</p> <p>cited in the application</p> <p>page 466, right-hand column, paragraph 2</p> <p>page 468, left-hand column, paragraph 5</p> <p>-page 470, right-hand column, paragraph 2; figure 3</p>	<p>1,3-11</p>
X	<p>---</p> <p>BOR LUEN TANG ET AL.: "ADAMTS: A novel family of proteases with an ADAM protease domain and thrombospondin 1 repeats"</p> <p>FEBS LETTERS, [Online] vol. 445, 26 February 1999 (1999-02-26), pages 223-225, XP002141413</p> <p>AMSTERDAM NL</p> <p>Retrieved from the Internet:</p> <p><URL:http://gdbwww.gdb.org/gdb-bin/genera/genera/hgd/Gene?!action=query&displayName=ADAMTS2> [retrieved on 2000-06-22]</p> <p>page 223, left-hand column, paragraph 2</p> <p>-page 225, right-hand column, paragraph 2; figure 2</p>	<p>1,3-11</p>
X	<p>---</p> <p>EMBL Database Entry AI378857</p> <p>Accession number AI378857; 28 January 1999</p> <p>ROBERT STRAUSBERG:"tc67h11.x1</p> <p>Soares_NhHMPu_S1 Homo sapiens cDNA clone"</p> <p>XP002141415</p> <p>the whole document</p> <p>---</p> <p>---</p>	<p>1,5-7</p>
	<p>---</p> <p>---</p>	

INTERNATIONAL SEARCH REPORT

International Application No

P /US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>FRANCISCA VÁZQUEZ ET AL.: "METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 33, 13 August 1999 (1999-08-13), pages 23349-23357, XP002141414</p> <p>MD US abstract</p> <p>page 23349, right-hand column, paragraph 2</p> <p>-page 23350, left-hand column, paragraph 1</p> <p>page 23351, left-hand column, paragraph 1</p> <p>-page 23352, right-hand column, paragraph 2; figure 1</p> <p>page 23353, left-hand column, paragraph 4</p> <p>-page 23357, left-hand column, paragraph 2</p> <p>-----</p>	<p>1,3-6, 8-11</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/06237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 22-27, 30, 33-35
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-12, 17-35 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 22-27, 30, 33-35

Present claims 22-27, 30 and 33-35 relate to an agent defined by reference to a desirable characteristic or property, namely decreasing or modulating expression or activity of an ADAMTS protein. The claims cover all agents having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any specific example of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agent by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 22-27, 30 and 33-35.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:1 or 23 encoding ADAMTS-2; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-2 polypeptide; ADAMTS-2 polypeptide of SEQ ID NO:2 or 24 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-2 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-2 protein

2. Claims: 36 and partially 1-12, 17-35

Polynucleotide of SEQ ID NO:3, 15 or 17 encoding ADAMTS-4; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-4 polypeptide; ADAMTS-4 polypeptide of SEQ ID NO:4, 16 or 18 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-4 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-4 protein

3. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:9 or 25 encoding ADAMTS-3; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-3 polypeptide; ADAMTS-3 polypeptide of SEQ ID NO:10 or 26 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-3 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-3 protein

4. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:13 or 21 encoding ADAMTS-5; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-5 polypeptide; ADAMTS-5 polypeptide of SEQ ID NO:13 or 21 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-5 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-5 protein

5. Claims: Partially, 1, 3-12, 17-35

Polynucleotide encoding an ADAMTS-9 protein of SEQ ID NO:27;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-9 polypeptide; ADAMTS-9 polypeptide of SEQ ID NO:27 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-9 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-9 protein

6. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:6 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:6 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

7. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:8 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:8 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

8. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:12 or 20 or variants thereof; ADAMTS polypeptide of SEQ ID NO:12 or 20 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein